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Original Article

Mesothelioma in Sweden: Dose–Response Analysis for Exposure to 29 Potential Occupational Carcinogenic Agents☆

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ABSTRACT

Background: There is little information on the dose–response relationship between exposure to occupational carcinogenic agents and mesothelioma. This study aimed to investigate this association as well as the existence of agents other than asbestos that might cause mesothelioma.
Methods: The Swedish component of the Nordic Occupational Cancer (NOCCA) study consists of 6.78 million individuals with detailed information on occupation. Mesothelioma diagnoses recorded in 1961–2009 were identified through linkage to the Swedish Cancer Registry. We determined cumulative exposure, time of first exposure, and maximum exposure intensity by linking data on occupation to the Swedish NOCCA job-exposure matrix, which includes 29 carcinogenic agents and corresponding exposure for 283 occupations. To assess the risk of mesothelioma, we used conditional logistic regression models to estimate hazard ratios and 95% confidence intervals.
Results: 2,757 mesothelioma cases were identified in males, including 1,416 who were exposed to asbestos. Univariate analyses showed not only a significant excess risk for maximum exposure intensity, with a hazard ratio of 4.81 at exposure levels 1.25–2.0 fb/ml but also a clear dose–response effect for cumulative exposure with a 30-, 40-, and 50-year latency time. No convincing excess risk was revealed for any of the other carcinogenic agents included in the Swedish NOCCA job-exposure matrix.
Conclusion: When considering asbestos exposure, past exposure, even for short periods, might be enough to cause mesothelioma of the pleura later in life.

1. Introduction

Mesothelioma is a very aggressive malignancy that occurs in the peritoneum or pleura. It is mainly linked to occupational asbestos exposure and was classified as an occupational disease in the 1950s [1]. Mesothelioma has a poor prognosis, with most cases dying within 1 year of diagnosis [2], and a long latency period of up to 40 years [3]. The incidence of mesothelioma varies; incidence in developed countries such as Belgium, Britain, and Australia exceeds 30 cases per 1 million inhabitants [4], and in Sweden, about 12 cases are diagnosed per 1 million inhabitants (approximately 120 cases/year) [5]. Between 1994 and 2008, 92,253 mesothelioma deaths were reported in 83 countries, 54% of them in Europe [6].

The risk of mesothelioma is strongest with exposure to asbestos types from the amphibole family. However, chrysotile (serpentine type) was the most common asbestos fiber used in Sweden [7]. In some industries, such as asbestos cement production, asbestos types from both the serpentine and amphibole families were used

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☆ **What's new**: In this study we conclude that there is a dose–response relationship between cumulative asbestos exposure and mesothelioma of the pleura in Sweden when we interpreted the univariate analysis model.

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[8]. Asbestos was banned in Sweden in 1982 [9], and there are strict precautions and security requirements for occupations that include the handling of or exposure to asbestos, e.g., asbestos removal [10]. Despite the fact that asbestos has been absent from the Swedish labor market for 35 years, the total annual number of new mesothelioma cases did not show any evidence of decline until the year 2014 [11].

Only a limited number of occupations have been reported to confer a significant excess risk of mesothelioma [12], and no connection between mesothelioma and any occupational exposure besides asbestos, such as air pollution [13], has been scientifically proven. In the United Kingdom and Finland, it has been estimated that 97% [14] and 90% [15] of mesothelioma cases, respectively, are related to asbestos exposure, mostly occupational asbestos exposure.

A recent report on the Nordic Occupational Cancer (NOCCA) cohort covered the period 1961–2005 and is the largest study of occupational cancer published so far in the Nordic countries. It included 2.8 million diagnosed cases of cancer in the five Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) and reported mesothelioma cases in occupations where asbestos exposure is not usually considered to be present [16]. A total of 40.6% of the mesothelioma cases in the NOCCA cohort were from Sweden (2,521 men and 548 women), and in 12 of the 53 occupations considered in this population, there was a statistically significant excess risk of mesothelioma among men [16].

There is little information about substances other than asbestos than can cause mesothelioma. Authors have found mesothelioma outcomes in animal studies after inhalation of refractory ceramic fibers [17], but no such effect on humans has been reported in the literature. Moreover, there is a lack of studies on the dose–response relationship between agents other than asbestos and mesothelioma, and the studies that do exist reported conflicting results [18–22].

We used the Swedish NOCCA-job exposure matrix (JEM) [23] to identify 29 potential occupational carcinogenic agents. Twenty-five of these agents are chemical agents, and four are non-chemical agents. In the present study, we linked the Swedish NOCCA-JEM with mesothelioma outcomes in the Swedish NOCCA study [16] to determine the existence of a dose–response relationship between occupational exposures and mesothelioma of the pleura.

2. Materials and methods

All people who participated in the 1960, 1970, 1980, and 1990 censuses in Sweden and were still alive and living in the country on 1 January of the year following the census were included in the study cohort. The individual data from these censuses are centrally computerized at the Swedish National Statistics office [24] and include information on economic activity, occupation, and industry. Personal identification numbers were used to link census data to the Swedish Cancer Registry to identify incident cases of mesothelioma of the pleura (7th revision of the International Classification of Diseases code 162.2) [25]. Linkage to the Total Population Registry was also carried out to obtain information on death and emigration.

All incident mesothelioma cases diagnosed from 1961–2009 were extracted from the NOCCA cohort. For each case, 10 controls were randomly selected among men born the same year who were alive and free from mesothelioma on the date of diagnosis of the case (hereafter referred to as the index date). As there were few women in occupations that included carcinogenic agents, we restricted our analyses to men in order to get better power. The Swedish NOCCA study received ethical approval from Forskningsetikkommitten at Karolinska Institutet (Dnr 03-466).

3. Exposure assessment and statistical analysis

The NOCCA-JEM [23] was developed specifically for the NOCCA study and was based on FINJEM [26]. Five separate NOCCA-JEMs were then developed, one for each of the Nordic countries included in the NOCCA study, as discussed in detail by Kauppinen et al. [23]. The Swedish NOCCA-JEM was used in the present study and contains 283 occupational categories with estimates of the prevalence and level of exposure to 29 occupational carcinogenic agents for four calendar periods: 1945–1959, 1960–1974, 1975–1984, and 1985–1994. Quantitative estimates of exposure to individual occupational carcinogenic agents and cumulative exposure to all 29 agents was calculated in 30,327 cases and matched controls from the Swedish NOCCA cohort (2,757 cases and 27,570 controls) by linking their occupations to the Swedish NOCCA-JEM.

Cases and controls started with an assigned occupational code that was based on the information recorded in the earliest census they completed, and this information was updated for each census. If occupational information changed at a subsequent census, the individual was assumed to have changed occupation in the middle of those two census years. Individuals who reported retirement in any census were recorded as such and considered only after the consensus date. The NOCCA-JEM gives mean group exposure for carcinogenic agents by occupation; therefore, we have no individual-level information on exposure or maximum intensity.

When estimating cumulative exposure, we assumed that the occupation that cases and controls reported in the 1960 census also applied up to 45 years prior to that census. To quantify cumulative exposure, we assigned a value of the product of the proportion and level of exposure ($P \times L$) from the Swedish NOCCA-JEM for each occupational category. This value was then multiplied by employment period, i.e., the time (T) in years during which the individual was in that occupation. This procedure was repeated for all agents in the Swedish NOCCA-JEM. Employment period was assumed to start at age 20 years and end at 65 years. When individuals had more than one occupation during the study period, the individual exposure history consisted of more than one $P \times L \times T$ value. Thus, cumulative exposure was estimated by summing the $P \times L \times T$ values over an individual's entire working career. We estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for each occupational carcinogenic agent by conditional logistic regression. We selected values corresponding to the 50th and 90th percentiles of cumulative exposure distribution among all exposed case/control individuals as cut-off points for categorization. Exposure values in the 0–50th percentile were categorized as "low," the 50-90th percentile as "moderate," and >90th percentile as "high". Individuals with zero exposure were used as the reference group. A test for trend was performed for a dose–response relationship between cumulative exposure and mesothelioma and individual agents and mesothelioma.

For asbestos, we present analyses among unexposed and ever-exposed individuals, with ever exposure distributed in categories of low, moderate, and high. Cumulative exposure to each occupational carcinogenic agent is reported in unit-years. Assuming that mesothelioma has a long latency period, i.e., the time between the beginning of asbestos exposure and mesothelioma diagnosis, and that recent exposures are less relevant than those which took place in the past, we performed additional analyses excluding all exposures that occurred 20–50 years before the index date of the cases and controls. This latency allowed us to compare our results to those of other studies [27]. Information on other potential confounders, such as smoking and alcohol consumption, were not available. Asbestos exposure <1.78 f/ml was categorized as low, 1.79–15.2 f/ml as moderate, and >15.2 f/ml as high and used in analysis for 0–50 years latency.

Table 1
Demographic characteristics of the pleural mesothelioma cases and controls

Characteristics	Cases	Controls
	N (%)	N (%)
Total number	2757 (100)	27570 (100)
Birth cohort		
1896–1910	418 (15.2)	4180 (15.2)
1910–1919	611 (22.2)	6110 (22.2)
1920–1929	708 (25.7)	7080 (25.7)
1930–1939	595 (21.6)	5950 (21.6)
1940–1949	386 (14.0)	3860 (14.0)
1950–1960	39 (1.40)	390 (1.40)
Age at index date (y)*		
<40	22 (0.8)	223 (0.8)
40–49	125 (4.5)	1247 (4.5)
50–59	442 (16.0)	4419 (16.0)
60–69	834 (30.3)	8341 (30.3)
70–79	970 (35.2)	9699 (35.2)
80+	364 (13.2)	3641 (13.2)
*Period of index date**		
1960–1969	105 (2.8)	1050 (2.8)
1970–1979	362 (9.7)	3620 (9.7)
1980–1989	948 (25.5)	9480 (25.5)
1990–1999	1202 (32.4)	12020 (32.4)
2000–2009	1099 (29.6)	10990 (29.6)

* Index date is defined as the date of diagnosis for the case in each case–control set.

Analysis for asbestos was also done for time since first exposure, divided in 0–9 years, 10–19 years, 20–29 years, 30–39 years, 40–49 years, and 50 + years. HRs and 95% CIs were used.

HRs and 95% CIs for pleural mesothelioma among men and maximum exposure intensity, defined by exposure index (P × L), were analyzed in four categories: 0 fb/ml, 0–0.1 fb/ml, 0.1–0.8 fb/ml, and 0.8–1.8 fb/ml. HRs were also analyzed for maximum exposure intensity (L) in four categories: 0 fb/ml, 0–0.2 fb/ml, 0.2–1.25 fb/ml, and 1.25–2 fb/ml.

4. Results

During follow-up, 2,757 mesothelioma cases and 27,570 controls were identified (Table 1). In the univariate model, 17 of the 29 occupational carcinogenic agents were statistically significantly associated with the risk of mesothelioma. Our study indicates that risk of mesothelioma is increased even at low levels of asbestos exposure. Cumulative doses of less than 1.78 f-y/ml led to an HR of 2.3. We found a dose–response relationship between cumulative asbestos exposure and mesothelioma of the pleura using a 30-year, 40-year, and 50-year lag time (i.e., latency period). We also found a significant excess risk after a 20-year latency period and with no latency period at all (latency = 0) (Table 2). There was no clear relationship between higher HR and time since first asbestos exposure. We observed a clear trend up to 49 years, but after 50 years it decreased (Table 3). On the other hand, we found a clear relationship between increased exposure intensity (exposure index) and for maximum exposure intensity and increased HRs (Tables 4 and 5). We found a clear relationship between maximum exposure intensity and increased HRs, with an HR of 4.81 for asbestos exposure levels 1.25–2.0 fb/ml. The asbestos part from the NOCCA-JEM [23] describing level (L) and probability (P) of exposure for occupations in 1945–1994 is shown in Table 6.

Nine other occupational carcinogenic agents had p <0.01 after adjustment for asbestos exposure (Table 7). The other 18 occupational carcinogenic agents did not show any excess risk or trend for mesothelioma of the pleura after adjustment for asbestos exposure. Moreover, after adjustment for asbestos exposure we found no significant excess risk for exposure to animal dust, benzene, chlorinated hydrocarbon solvents, crystalline silica, formaldehyde, methylene chloride, other organic solvents, toluene, wood dust, ionizing radiation, or perceived physical workload. Aliphatic and alicyclic hydrocarbon solvents, diesel exhaust, gasoline,

Table 2
Hazard ratios (HR) and 95% confidence intervals (95% CI) for asbestos exposure (ASB) and pleural mesothelioma among men

Lag time, ASB level	Number of individuals		HR	95% CI
	Cases	Controls		
Lag = 0				
Ever exposed	*1416*	*7896*	*2.65*	*2.45–2.87*
None	1341	19674	1.00	Ref.
Low	600	3979	2.24	2.02–2.48
Moderate	669	3115	3.17	2.86–3.50
High	147	802	2.61	2.16–3.15
			$p < 0.01$	
Lag = 20				
Ever exposed	*1327*	*7209*	*2.68*	*2.46–2.90*
None	1430	20361	1.00	Ref.
Low	549	3564	2.25	2.02–2.51
Moderate	673	3153	3.07	2.78–3.92
High	105	492	3.01	2.41–3.76
			$p < 0.01$	
Lag = 30				
Ever exposed	*1159*	*6037*	*2.69*	*2.47–2.92*
None	1598	21533	1.00	Ref.
Low	508	3045	2.34	2.09–2.62
Moderate	598	2797	2.95	2.66–3.28
High	53	195	3.77	2.76–5.16
			$P < 0.01$	
Lag = 40				
Ever exposed	*871*	*4330*	*2.70*	*2.46–2.96*
None	1886	23240	1.00	Ref.
Low	462	2502	2.48	2.20–2.79
Moderate	391	1787	2.92	2.58–3.31
High	18	41	5.88	3.33–10.3
			$p < 0.01$	
Lag = 50				
Ever exposed	*489*	*2480*	*2.44*	*2.16–2.75*
None	2268	25090	1.00	Ref.
Low	346	1793	2.37	2.06–2.72
Moderate	141	683	2.59	2.12–3.15
High	2	4	6.21	1.14–34.0
			$p < 0.01$	

ASB is categorized based on 50th and 90th percentile of cumulative exposure distribution among exposed mesothelioma cases and controls.
Asbestos exposure <1.78 f/ml was categorized as low, 1.79–15.2 f/ml as moderate, and >15.2 f/ml as high.

Table 3
Hazard ratios (HR) and 95% confidence intervals (95% CI) for pleural mesothelioma among men, by time since first asbestos exposure

Years since first exposure	Number of individuals		HR	95% CI
	Cases	Controls		
Never exposed	1341	19674	1.00	Ref.
>0–9	18	142	1.74	1.05–2.88
10–19	71	542	1.86	1.43–2.41
20–29	168	1174	2.05	1.71–2.45
30–39	288	1708	2.49	2.14–2.90
40–49	382	1850	3.26	2.83–3.75
50+	489	2480	2.86	2.53–3.22

Table 4
Hazard ratios (HR) and 95% confidence intervals (95% CI) for pleural mesothelioma among men, by maximum intensity*

Maximum intensity	Number of individuals		HR	95% CI
	Cases	Controls		
0 fibres/ml	1341	19674	1.00	Ref.
>0–0.2 fibres/ml	672	4391	2.27	2.06–2.51
>0.2–1.25 fibres/ml	543	2886	2.26	2.48–3.07
>1.25–2.0 fibres/ml	201	619	4.81	4.06–5.70

* Maximum intensity is categorized based on the 50th and 90th percentile of exposure distribution among exposed cases and controls.

Table 5
Hazard ratios (HR) and 95% confidence intervals (95% CI) for pleural mesothelioma among men, by maximum intensity*, probability (P) × level (L) (exposure index)

Maximum intensity	Number of individuals		HR	95% CI
	Cases	Controls		
0 fibres/ml	1341	19674	1.00	Ref.
>0–0.1 fibres/ml	665	4348	2.27	2.06–2.51
>0.1–0.8 fibres/ml	724	3516	3.02	2.74–3.33
>0.8–1.8 fibres/ml	27	32	12.7	7.58–21.4

* Maximum intensity is categorized based on the 50th and 90th percentile of exposure distribution among exposed cases and controls.

perchloroethylene, sulfur dioxide, 1,1,1-trichloroethane, and night-work had $p > 0.01$ and were also omitted.

Just 55.3% of the cases of mesothelioma of the pleura in our study were rated for asbestos exposure in the Swedish NOCCA-JEM. The number of women was too few to permit an analysis by gender.

5. Discussion

We studied the dose–response relationship between exposure to 29 occupational agents classified as carcinogens by the International Agency for Research on Cancer [28] and the risk of mesothelioma of the pleura. Our important findings were a clear relationship between maximum exposure intensity and increased HR, with an HR of 4.81 for asbestos exposure levels 1.25–2.0 fb/ml. We found a dose–response relationship in univariate analyses between asbestos exposure and mesothelioma of the pleura with a 30-, 40-, and 50-year latency period. Our study indicates that risk of mesothelioma is increased even at low levels of asbestos exposure. Cumulative doses of less than 1.78 f-y/ml led to an HR of 2.3. The threshold limit value (TLV) for asbestos in 1976 was 2 f/ml, which means that 1 year of exposure around the TLV was considered a risk. In 1982, the Swedish Agency of Working Life dramatically decreased the TLV to 0.5 f/ml and again in 1987 to 0.2 f/ml [29–31].

Previous studies on the dose–response relationship between asbestos exposure and the risk of mesothelioma have shown mixed results. Some found no clear relationship [20–22], whereas Rodgers et al. [18] and Lacourt et al. did find a dose–response relationship [19]. A later case–control study of mesothelioma and cumulative asbestos exposure found that the impact of a given increase in dose depended on when the dose was received [32]. Järvholm et al. [33] observed a significant excess risk of mesothelioma among construction workers exposed to multiple carcinogenic agents, including asbestos and bitumen. We were unable to control for other potential confounding factors or effect modifiers such as smoking.

Nine occupational carcinogenic agents showed an excess risk of mesothelioma of the pleura after adjustment for asbestos exposure, with a $p < 0.01$. However, welding fumes, trichloroethylene, lead, aromatic hydrocarbon solvents, and benzo(a)pyrene showed a positive significant trend, but this was probably due to misclassification. Most of the 10 agents in Table 7 occur in industries in which asbestos was handled, but the Swedish NOCCA-JEM is not sensitive enough to separate those exposures, as its occupational classification is unspecific in many groups e.g., mechanics. Asbestos exposure has probably occurred as background exposure at low levels in many mechanical industries, but the JEM just classify occupations where asbestos have been handled.

Table 6
Probability (P) and level (L) of asbestos exposure (fibers/ml) according to SWEJEM, by occupation and time period

NYK	Title	1945–1959		1960–1974		1975–1984		1985–1994	
		P	L	P	L	P	L	P	L
631	Railway engine drivers and assistants	80	0.20	80	0.20	0	0.00	0	0.00
731	Furnacemen	5	0.05	5	0.05	5	0.01	5	0.01
751	Machinery fitters, machine assemblers	51	0.20	53	0.20	25	0.05	2	0.01
753	Sheet metal workers	30	2.00	30	1.00	30	0.20	0	0.00
754	Plumbers and pipe fitters	56	0.50	56	0.30	30	0.20	1	0.10
755	Welders and flame cutters	40	2.00	40	1.00	25	0.20	0	0.00
761	Electrical fitters and wiremen	40	0.03	50	0.04	10	0.02	2	0.01
769	Nonspecified electrical and electronics work	10	0.03	20	0.05	15	0.02	0	0.02
771	Construction carpenters and joiners	40	0.50	70	1.00	30	0.40	2	0.10
781	Painters	10	0.05	25	0.14	10	0.05	2	0.02
791	Bricklayers	40	0.30	50	0.31	30	0.10	5	0.05
794	Insulators	90	2.00	89	1.50	70	2.00	50	0.08
793	Concrete and construction workers	40	1.00	80	1.00	25	0.40	1	0.02
799	Nonspecified other building and construction work	10	1.00	21	1.25	10	0.40	2	0.06
811	Glass formers and cutters	20	0.20	20	0.20	15	0.10	0	0.00
836	Paper and paperboard workers	20	0.01	20	0.01	10	0.01	0	0.00
838	Chemical and cellulose processing work n.e.c.	5	0.08	5	0.06	5	0.05	0	0.00
872	Crane and hoist operators	25	0.10	25	0.10	25	0.10	0	0.00
873	Riggers and cable splicers	41	0.08	41	0.08	20	0.02	0	0.00
883	Store and warehouse workers	0	0.00	3	0.02	0	0.02	0	0.00
933	Chimney sweeps	80	0.10	80	0.10	80	0.02	80	0.00

NYK = Nordisk Yrkesklassificering.

Table 7
Asbestos (ASB) adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) for exposure to selected agents/nonchemical factors and pleural mesothelioma among men

Agent/factor, level	Number of individuals		Unadjusted for ASB		Adjusted for ASB	
	Cases	Controls	HR	95% CI	HR	95% CI
Aromatic hydrocarbon solvents						
Ever exposed	267	2164	1.26	1.10–1.44	1.12	0.98–1.29
None	2490	25406	1.00	Ref.	1.00	Ref.
Low	118	1114	1.08	0.89–1.31	1.06	0.87–1.29
Moderate	109	843	1.32	1.08–1.62	1.13	0.92–1.40
High	40	207	1.98	1.41–2.79	1.37	0.96–1.94
			$p < 0.01$		$p = 0.05$	
Benzo(a)pyrene						
Ever exposed	644	4238	1.69	1.54–1.86	1.12	1.01–1.24
None	2113	23332	1.00	Ref.	1.00	Ref.
Low	297	2131	1.56	1.36–1.78	1.06	0.92–1.22
Moderate	284	1685	1.86	1.63–2.13	1.16	1.01–1.34
High	63	422	1.64	1.26–2.15	1.23	0.93–1.61
			$p < 0.01$		$p = 0.01$	
Bitumen fumes						
Ever exposed	46	414	1.11	0.82–1.52	1.06	0.78–1.45
None	2711	27156	1.00	Ref.	1.00	Ref.
Low	12	222	0.54	0.30–0.97	0.58	0.32–1.04
Moderate	10	174	0.58	0.30-1.09	0.54	0.28–1.03
High	24	18	13.20	7.17–24.33	8.45	4.47–15.96
			$p < 0.01$		$p < 0.01$	
Chromium						
Ever exposed	1027	5660	2.34	2.15–2.54	1.55	1.41–1.71
None	1730	21910	1.00	Ref.	1.00	Ref.
Low	589	2744	2.77	2.50–3.07	1.67	1.49–1.88
Moderate	373	2322	2.07	1.83–2.33	1.50	1.32–1.71
High	65	594	1.41	1.09–1.83	1.21	0.93–1.57
			$p < 0.01$		$p < 0.01$	
Iron						
Ever exposed	952	5019	2.41	2.21–2.62	1.61	1.46–1.77
None	1805	22551	1.00	Ref.	1.00	Ref.
Low	473	2499	2.42	2.16–2.70	1.55	1.37–1.75
Moderate	353	2035	2.19	1.93–2.47	1.62	1.42–1.85
High	126	485	3.19	2.61–3.90	1.83	1.45–2.31
			$p < 0.01$		$p < 0.01$	
Lead						
Ever exposed	1135	6686	2.23	2.05–2.42	1.52	1.39–1.67
None	1622	20884	1.00	Ref.	1.00	Ref.
Low	506	3387	1.98	1.78–2.21	1.50	1.33–1.68
Moderate	519	2621	2.59	2.32–2.88	1.57	1.39–1.77
High	110	678	2.03	1.64–2.50	1.44	1.16–1.79
			$p < 0.01$		$p < 0.01$	
Nickel						
Ever exposed	952	5015	2.41	2.21–2.62	1.61	1.46–1.77
None	1805	22555	1.00	Ref.	1.00	Ref.
Low	530	2450	2.77	2.49–3.08	1.85	1.65–2.08
Moderate	356	2031	2.22	1.96–2.51	1.48	1.30–1.69
High	66	534	1.55	1.20–2.02	0.98	0.75–1.29
			$p < 0.01$		$p < 0.01$	
Trichloroethylene						
Ever exposed	514	2929	1.94	1.75–2.16	1.66	1.49–1.85
None	2243	24641	1.00	Ref.	1.00	Ref.
Low	218	1513	1.59	1.37–1.85	1.31	1.12–1.53
Moderate	233	1154	2.23	1.92–2.59	1.91	1.64–2.22
High	63	262	2.60	1.96–3.46	2.61	1.95–3.50
			$p < 0.01$		$p < 0.01$	
Welding fumes						
Ever exposed	952	5019	2.41	2.21–2.62	1.61	1.46–1.77
None	1805	22551	1.00	Ref.	1.00	Ref.
Low	347	2606	1.69	1.50–1.91	1.42	1.25–1.62
Moderate	467	1935	3.03	2.71–3.39	1.75	1.53–2.00
High	138	478	3.57	2.94–4.33	2.03	1.61–2.56
			$p < 0.01$		$p < 0.01$	
Ultraviolet radiation						
Ever exposed	978	9785	1.00	0.92–1.08	0.65	0.59–0.71
None	1779	17785	1.00	Ref.	1.00	Ref.
Low	584	4799	1.22	1.11–1.35	0.74	0.67–0.83
Moderate	326	4118	0.78	0.69–0.89	0.53	0.46–0.61
High	68	868	0.77	0.60–1.00	0.50	0.39–0.66
			$p < 0.01$		$p < 0.01$	

Exposures are categorized based on 50th and 90th percentile of cumulative exposure distribution among exposed mesothelioma cases and controls.

The high HR we observed in the highest exposure category of bitumen fumes was unexpected. Bitumen exposure is common among asphalt workers, but this group is generally exposed to multiple agents, as are workers in many other occupations. In some occupations, individuals were classified for both bitumen and asbestos exposure, e.g., insulators and chemical and cellulose process workers; thus, we cannot exclude the possibility of misclassification.

The association we found between exposure to trichloroethylene and the risk of mesothelioma of the pleura was also unexpected, and the mechanism behind it is unclear. Simultaneous exposure to asbestos and other occupational carcinogenic agents or misclassification of occupations/exposures cannot be entirely ruled out. Another limitation of the Swedish NOCCA-JEM is that occupation/exposure was only available every 10 years. Moreover, a JEM is a rather crude tool for exposure assessment, as occupations are only surrogates of exposure. Some occupations have high exposure prevalence, e.g., painters for solvent exposure during the 1960s and 1970s, and are a good fit for the JEM, whereas others are more complicated. Mechanics or process workers are large occupational groups with different or multiple exposures, which can lead to lower exposure prevalence and an increased risk of misclassification. Ship building workers and dock workers are also included in this group. A proportion of the mechanics in the mechanical industry have been exposed to trichloroethylene through degreasing and to asbestos fibers through other activities. There are 283 occupations in the NOCCA-JEM, but only 21 of them had a relevant prevalence of asbestos exposure. Each occupational category consists of a large number of job titles, some of which could be exposed to asbestos but were diluted in the occupational category and did not fulfill our definition of exposure in the Swedish NOCCA-JEM. Other occupations had broad definitions. This misclassification can bias HRs towards the null.

Asbestos was banned in Sweden in 1982 [9], after which exposure levels and the number of exposed individuals decreased dramatically. We chose a 50-year latency period in our analysis due to the exposure pattern in the Swedish NOCCA-JEM, which ended in 1994. The latency time for mesothelioma is up to 40 years [33,34].

We used rather simple rules: The variable must be either statistically significantly associated or consistently associated with mesothelioma, and it could not be highly correlated with other variables. Consistency means the levels of exposure should show a dose–response relationship, i.e., variables should be rational considering their effect on cancer.

The main limitation of our study is the inevitable potential for exposure misclassification, which may arise from two sources. First, JEMs cannot account for exposure heterogeneity within jobs in an occupational category [35]. Second, because work history in our study was based on census records, we had information on profession only every 10 years; we did not know about every change in occupation that might have happened between the censuses.

We found the pattern in time/years since first exposure to asbestos; the highest group (aged 50 + years) had a weaker relationship. That may be due to the insufficient nature of older information. Maximum exposure intensity was the analysis that confirmed a dose–response relationship between asbestos exposure and pleura mesothelioma. However, this study supports the existence of a dose–response relationship between asbestos exposure with risk of mesothelioma of the pleura.

6. Conclusions

We observed a significant, dose–response relationship between maximum intensity asbestos exposure and mesothelioma of the

pleura and cumulative asbestos exposure with 30-, 40-, and 50-years lag time. Cumulative exposure to asbestos, even at low levels, entailed an increased risk of mesothelioma of the pleura, indicating that even short periods with cumulative doses <1.78 f-y/ml can increase the risk of mesothelioma. Time since first exposure did not show any sufficient dose–response relationship in the longest lag period (>50 years).

Conflicts of interest

The authors have no competing interests to declare.

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