The Risk of Lung Cancer After Cessation of Asbestos Exposure in Construction Workers Using Pleural Malignant Mesothelioma as a Marker of Exposure

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Objective: To study the risk of lung cancer in heavily asbestos-exposed workers after the exposure to asbestos has ended. **Methods:** Lung cancer was studied in a cohort of 189,896 Swedish construction workers through a linkage with the Swedish Cancer Registry. Asbestos exposure was estimated by the incidence of malignant mesothelioma in the occupational group. **Results:** There were in total 2835 cases of lung cancer. Workers with heavy exposure to asbestos had an increased risk of lung cancer (relative risks = 1.74; 95% confidence interval, 1.25 to 2.41) before exposure ended and a similar risk to those with low exposure 20 years after the exposure had ceased (relative risks = 0.94; 95% confidence interval, 0.77 to 1.15). **Conclusions:** Workers with heavy exposure to asbestos have a similar risk of lung cancer as persons with low or no exposure 20 years after the exposure has ended.

Asbestos is a well-established cause of mesothelioma and lung cancer.¹ It is generally accepted that the risk of mesothelioma persists and increases a long time after exposure to asbestos has ended.^{2–6} Less is known if the risk of lung cancer changes when the exposure to asbestos ceases. Some studies indicate that the risk decreases some years after the exposure has ended.^{7–10} Results from studies based on industrial cohorts are hard to evaluate because the workers may have been exposed in other industries after leaving the industry because the use of asbestos has been common in many industries, for example, the construction manufacturing industry and shipyard industry. The risk of asbestos was highlighted in Sweden in the 1970s, and the import of asbestos decreased sharply (Fig. 1). Some industries, such as the shipyard and construction industries, decreased the use of asbestos in the mid-1970s after agreements between employers and unions. Asbestos was prohibited to use by a law in 1982.¹¹ Subsequently, the exposure of almost all Swedish workers ended in the early 1980s. This gives an opportunity to study the risk of lung cancer after cessation of exposure. Even if a Swedish worker changed job and employer after the early 1980s, there was almost no exposure to asbestos.

The risk of lung cancer varies between occupational groups depending on the level of exposure to asbestos. Also, the risk of mesothelioma depends on the level of asbestos exposure. Because the risk of mesothelioma does not decrease after exposure to asbestos has ended, it can be used as a marker of exposure also several years after the exposure has ended. Furthermore, it does not depend on changes in smoking habits, whereas the risk of lung cancer due to asbestos exposure interacts with smoking.¹

The objective of this study was to investigate whether the risk of lung cancer decreases after the exposure to asbestos has ended. We compared the risk of lung cancer in construction workers with low and high exposures to asbestos before and after the exposure has ended. The incidence of pleural malignant mesothelioma in the occupational groups was used as a marker of exposure to asbestos, that is, a high incidence of mesothelioma indicates a high exposure to asbestos.

MATERIALS AND METHODS

The analysis is based on a cohort of workers in the Swedish construction industry who participated in health examinations between 1971 and 1993. The examinations were free of charge and offered all construction workers in the country according to an agreement between unions and employers associations. It is estimated that about 80% of the workers participated at least once. As previously described, some data from the examinations, as, for example, smoking habits and job title, were computerized.¹² The job titles were merged to 22 major groups by technical staff in the industry in the mid-1970s. The computerized register of construction workers who had participated in health examinations was reorganized in 1990s, and persons who could not be identified in official registers were excluded (0.1%). The register contains after exclusion 389,132 persons. About 5% workers of the cohort were women ($N = 19,418$), and most have not been heavily exposed to asbestos and they were excluded in the analysis. Men who were younger than 15 years ($N = 1$) or older than 65 years ($N = 1725$) at the first examination were excluded because very young persons rarely were hired by the industry and the age of retirement has been 65 years since 1976. Incident cases of lung cancer or pleural mesothelioma were found from a linkage with the Swedish Cancer Register. Year of death and emigration were collected from a linkage with official Swedish registries. In the analysis, we used information from the first health examination about job title and started the follow-up the year after the first examination. The linkage with registers was from January 1, 1971, through December 31, 2011. Person-years were calculated for each individual from the year after the first health examination, until 2011, death, emigration, or occurrence of cancer (lung cancer and mesothelioma, respectively). The relative risks (RRs) were calculated by the Poisson regression [$\log(\text{number of cases group } k) = A_k \cdot \text{exposure} + B_i \cdot \text{age-group} + C_j \cdot \text{smoking habits} + \log(\text{person-years group } k)$], where age-group and smoking habits are categorical variables and $\log(\text{person-years})$ is an offset variable; exposure is 0 for the reference group and 1 for the exposed group k ; $RR_k = \exp(A_k)$] using the incidence rate in the low-exposed group in the latest time period (2001 to 2011) as reference group. Standard incidence ratios (SIRs) were calculated from national statistics of incidence rates stratified for sex, age, and calendar year.

Exposure Assessment

To estimate the exposure to asbestos, we calculated the incidence of pleural mesothelioma in the occupational groups. This analysis was restricted to ages between 40 and 84 years and adjusted for age (5-year classes) and birth cohort (10-year classes) according to the distribution of person-years among salaried employees. This

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FIGURE 1. The import of raw asbestos to Sweden.

TABLE 1. Asbestos Exposure Categorized According to Occurrence of Pleural Mesothelioma 1972 to 2011 in Occupational Groups in the Cohort of Construction Workers

Exposure to Asbestos	Occupational Group	N	Cases	Incidence Rate*
High	Insulators	1,617	15	39.9
	Plumbers and pipefitters	16,818	69	17.9
	Electricians	19,520	49	12.8
	Sheet-metal workers	6,467	16	12.5
	Roofers	836	1	12.2
	Floor layers	3,203	6	10.0
Medium	Refrigeration repairers	669	2	9.9
	Painters	16,401	30	7.9
	Drivers	4,047	7	7.3
	Concrete workers	30,718	48	6.8
	Foremen	25,094	36	5.9
	Others	30,513	40	5.9
	Wood workers	44,154	54	5.8
	Glaziers	1,625	1	4.6
	Repairers	2,112	2	4.0
Low	Salaried employees	10,170	10	3.8
	Brick-layers	8,175	8	3.6
	Earthmoving workers	8,923	6	3.2
	Crane operators	3,065	3	3.0
	Machine operators	8,752	2	0.8
	Rock workers	3,283	1	0.6
	Asphalt workers	2,898	0	0.0
Total		249,060	406	

*Per 100,000 person-years (adjusted to age and birth cohort).

analysis included 249,060 men (Table 1). Very old persons (85+ years) were excluded because diagnosis may have less precision in very high ages.

Lung Cancer

Persons born in 1955 or later were excluded in the analysis because they started to work in the mid-1970s or later when there was a considerable decrease in the use of asbestos. We restricted the analysis to men who had been examined between 1971 and 1980 because the use of asbestos decreased rapidly in the mid-1970s. In the analysis of lung cancer, we considered only person-years

between 40 and 74 years because lung cancer is rare before the age of 40 years. The decision to exclude men who are 75 years or older was that less than 10 years should have elapsed after the retirement. The analysis of lung cancer was adjusted for age and smoking habits. The smoking habits were classified into nonsmokers, ex-smokers, moderate smokers (less than 15 cig/day, less than 8 cigars or 100 g or more pipe tobacco/week), and heavy smokers from the first health examinations. If data were missing at the first examination, smoking habits from the second or third examination were used if available. Persons with unknown smoking habits were excluded (7.5%). The analysis of lung cancer included 189,796 men.

We stratified the analysis of lung cancer in the following four decades: 1972 to 1980, 1981 to 1990, 1991 to 2000, and 2001 to 2011. Standard incidence ratios for lung cancer were calculated from national incidence rates adjusting for age-group and calendar year (Table 3) using a Poisson distribution to calculate 95% confidence intervals (CIs).

The statistical package SAS 9.3 (SAS Institute Inc., Cary, NC) was used for the Poisson regression analyses using the Wald statistics to estimate 95% CI. This study was approved by the regional Ethical review board (2010/326-32M).

RESULTS

There were 406 cases of pleural mesothelioma (Table 1). Men in jobs with incidence rates of pleural mesothelioma more than 10 per 100,000 person-years were classified as heavy exposed to asbestos, those with an incidence between 5.0 and 9.9 as medium exposed, and those less than 5.0 as low exposed (Table 1).

There were in total 2835 cases of lung cancer included in the analysis (Table 2). During the 1970s, the risk of lung cancer was increased in groups with heavy or medium asbestos exposure as expected, whereas from the 1990s the risk for lung cancer was similar between the exposure groups (Table 3 and Fig. 2). The RRs are compared with the risk in the low-exposed group in the last decade (2001 to 2011). The risk of lung cancer in the low-exposed group did not show any clear change over the decades, whereas the RRs in heavy- and medium-exposed groups showed a declining risk. For example, the RR for heavy-exposed workers decreased from 1.74 in 1972 to 1980 to 0.94 in 2001 to 2011. The incidence rates of lung cancer among the construction workers have also been

TABLE 2. Number of Lung Cancer Cases in the Occupational Groups 1972 to 2011 in the Cohort of Construction Workers Categorized According to Asbestos Exposure in Table 1

Exposure to Asbestos	Occupational Group	N	Cases
High	Insulators	1,207	24
	Plumbers and pipefitters	13,512	247
	Electricians	14,559	147
	Sheet-metal workers	4,722	65
	Roofers	617	19
	Floor layers	2,369	45
Medium	Refrigeration repairers	421	11
	Painters	13,532	193
	Drivers	2,890	41
	Concrete workers	25,571	503
	Foremen	19,143	270
	Others	19,556	312
	Wood workers	35,901	395
	Glaziers	1,231	20
Low	Repairers	1,446	28
	Salaried employees	6,564	86
	Brick-layers	6,642	94
	Earthmoving workers	6,496	104
	Crane operators	2,427	56
	Machine operators	6,033	81
	Rock workers	2,655	54
	Asphalt workers	2,302	40
	Total	189,796	2,835

TABLE 3. Age and Smoking Adjusted Relative Risks (RRs*) of Lung Cancer in the Cohort of Construction Workers According to Asbestos Exposure and Time Period and SIR†

Asbestos Exposure	1972–1980				1981–1990				1991–2000				2001–2011			
	Cases	RR* (95% CI)	SIR† (95% CI)	SIR† (95% CI)	Cases	RR (95% CI)	SIR (95% CI)	SIR (95% CI)	Cases	RR (95% CI)	SIR (95% CI)	SIR (95% CI)	Cases	RR (95% CI)	SIR (95% CI)	SIR (95% CI)
Low	44	1.06 (0.76–1.47)	0.70 (0.52–0.93)	0.70 (0.52–0.93)	146	1.22 (0.98–1.51)	0.88 (0.75–1.04)	0.88 (0.75–1.04)	177	1.12 (0.92–1.38)	0.77 (0.67–0.90)	0.77 (0.67–0.90)	196	1 (reference)	0.83 (0.72–0.96)	0.83 (0.72–0.96)
Medium	223	1.41 (1.17–1.72)	0.89 (0.78–1.01)	0.89 (0.78–1.01)	488	1.26 (1.07–1.49)	0.89 (0.82–0.98)	0.89 (0.82–0.98)	523	1.23 (1.04–1.45)	0.80 (0.74–0.88)	0.80 (0.74–0.88)	491	0.92 (0.78–1.09)	0.70 (0.64–0.77)	0.70 (0.64–0.77)
Heavy	44	1.74 (1.25–2.41)	1.19 (0.88–1.60)	1.19 (0.88–1.60)	126	1.53 (1.22–1.92)	1.09 (0.92–1.30)	1.09 (0.92–1.30)	176	1.30 (1.06–1.59)	0.84 (0.72–0.96)	0.84 (0.72–0.96)	201	0.94 (0.77–1.15)	0.74 (0.65–0.85)	0.74 (0.65–0.85)

*Relative risk (95% CI), estimated from the Poisson regression analysis adjusted for age and smoking habits (for details, see the Materials and Methods section).

†Standard incidence ratio (95% CI) based on national incidence rates, adjusted for sex, age, and calendar year.

CI, confidence intervals; RR, relative risk; SIR, standard incidence ratio.

FIGURE 2. The relative risk of lung cancer according to time period and exposure level.

compared with the incidence rates in the general population adjusted for age and time period and are shown as SIR. The SIRs show a similar time pattern, that is, a declining SIR in heavy- and medium-exposed groups. The SIRs were not adjusted to smoking habits, and an SIR less than 1 may indicate lighter smoking habits among the construction workers than in the general population.

DISCUSSION

This study shows that the risk of lung cancer was dependent on exposure to asbestos in the 1970s because those with high exposure had a higher risk than those with low exposure. Nevertheless, when about 20 years have elapsed since last exposure, there was similar risk for lung cancer among those with high and low exposures (Fig. 2). This is a similar time pattern as for lung cancer caused by tobacco smoking, where the risk after about 10 years starts to decrease in ex-smokers compared with current smokers and continues to decrease during several decades.^{13,14}

Our findings are similar to some other studies. A Swedish study of shipyard workers, mainly exposed to chrysotile, did not show any increased risk of lung cancer 7 to 15 years after the cessation of asbestos even though the pleural mesothelioma incidence was high. Nevertheless, the power was low and an elevated risk could not be excluded.¹⁰ An Italian study of chrysotile and crocidolite cement workers found that the risk of lung cancer was significantly decreased 15+ years since last exposure compared with 3 to 15 years after last exposure (15 to 30 years $RR = 0.70$; 30+ years $RR = 0.56$).⁹ Nevertheless, the risk was also lower during the first 3 years after the exposure had ended ($RR = 0.38$; 95% CI, 0.22 to 0.65). The authors pointed out that there were no other asbestos factories in the area after the plant closed in 1986, which they considered made asbestos exposure among the workers unlikely thereafter. A German case-control study conducted in 1988 to 1996 showed that the odds ratio declined to half after 20 years or more after last exposure compared with 0 to 19 years after exposure.⁸ Another Italian study of textile workers, heavily exposed to various types of asbestos including crocidolite, studied lung cancer in subjects younger than 80 years. It showed that the RR for lung cancer was significantly increased in three periods after last employment (less than 15, 15 to 25 and 25+ years since last employment, Standardized mortality ratio: 302, 363, and 278, respectively).¹⁵ It is not known if the factory workers took another asbestos-related job after leaving the plant.

There are some strengths and weakness of this study. It is a prospective study, where the information about exposure is not de-

pendent on estimations from the workers. It is large and has power to detect moderate increased/decreased risks. The exposure assessment is based on occupational title, and there may be some nondifferential misclassification, which may decrease the difference in risk between the groups.

The incidence of pleural malignant mesothelioma is almost entirely caused by exposure to asbestos and should be a good marker of asbestos exposure. Nevertheless, amphiboles have a higher potency to cause mesotheliomas than chrysotile, whereas the difference in potency for causing lung cancer is less clear.¹⁶ Chrysotile has been the major asbestos used in Swedish construction industry. If some occupational groups had more exposure to amphiboles, and we use mesothelioma as a marker of total exposure to asbestos, such groups' total exposure to asbestos would be overestimated. Spraying of asbestos usually meant the use of amosite and insulators was the group spraying asbestos, meaning that the total exposure of asbestos could be overestimated. It is, however, a rather small group, and exclusion of them from the analysis did not substantially change the results.

We do not know the exact time when every worker stopped being exposed to asbestos, which also may contribute to some non-differential misclassification. If workers who got lung cancer end exposure to asbestos at the time of diagnosis, there is a linkage between disease and cessation of exposure. Nevertheless, it is a small proportion of workers who got the diagnosis, and the bias will be small. The smoking habits were similar in the exposure groups, 29% to 32% were nonsmokers, 21% ex-smokers, 35% to 36% moderate smokers, and 11.5% to 13.5% heavy smokers, which decrease the risk of residual confounding after adjustment in analyses for smoking habits. They were determined at the first health examination and may have changed over time. If the smoking habits changed differently over time between exposure categories, it may cause bias. Although we cannot exclude such bias, we consider it less likely because most workers have similar socioeconomic background, were subject to similar antismoking campaigns, and had similar access to health care. There are also exposure to other lung carcinogens in the construction industry, for example, diesel exhaust and silica. If exposure to such agents has changed differently over time in persons with low- and high-exposure asbestos, it may introduce bias. Nevertheless, we think that this is less probably because groups with high exposure to asbestos have rather low exposure to silica and diesel exhausts compared with some occupational groups with low exposure to asbestos.

The workers in the Swedish construction industry have mainly been exposed to chrysotile. Also, amosite has been used to some extent, for example, for spray insulation. Amphiboles seem to have a higher potency than chrysotile to cause mesothelioma, but it is less clear if there is any different potency to cause lung cancer.¹⁶ Some studies of humans and animals have indicated that inhaled chrysotile has shorter retention in the lungs than amphiboles.^{17,18} We cannot separately analyze workers with exposure to different types of asbestos, and it is not possible to draw conclusions if the risk of lung cancer in workers with a heavy exposure to amphiboles has another time pattern after cessation of exposure.

Thus, the time pattern of lung cancer risk in workers exposed to asbestos is different from the pattern of pleural mesothelioma. The difference may depend on differences in retention of fibers and interaction with smoking. Lung cancers in humans are often situated in central airways and around bifurcations. The clearance of the fibers may be faster than for fibers that have reached the pleura. Smoking interacts with asbestos in causing lung cancer, but the risk for mesothelioma is similar for smokers and non-smokers. The mechanisms by which asbestos cause lung cancer are not established. It seems to cause lung cancer both with and without concomitant exposure to tobacco smoke. Experiments in animals have indicated genotoxicity at very high doses, but other mechanisms may be more important at lower exposure, for example, epigenetic mechanisms and enhancing the delivery of polycyclic aromatic hydrocarbons into cells.¹⁹ Tobacco smoking and asbestos interact as causes of lung cancer.²⁰ A possible mechanism for this interaction is that asbestos enhance the transport of tobacco carcinogens as polycyclic aromatic hydrocarbons into the cell. This interaction may decrease when the exposure to asbestos stops because chrysotile fibers are more rapidly cleared from the lungs.

The finding that the risk of lung cancer is similar between the groups 20 years after the exposure has ended has implication for future epidemiological studies of lung cancer. If there are similar time patterns also for other lung carcinogens, the risk may be underestimated if the analysis is not adjusted for time since last exposure. Because lung cancer incidence increases by age, most cases occur in higher ages when persons may have left the exposed job. A modest increased risk during or shortly after exposure may then be difficult to detect because the majority of cases will occur long time after the exposure has ended.

CONCLUSIONS

This study shows that workers with an increased risk of lung cancer during high exposure to asbestos have similar risk as low-exposed workers 20 years after the exposure has ended, but their risk of mesothelioma is still higher 20 years later. This indicates that the mechanisms of carcinogenicity for asbestos are different for lung cancer and mesothelioma.

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