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The risk of lung cancer and mesothelioma after cessation of asbestos exposure: a prospective cohort study of shipyard workers

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The risk of lung cancer and mesothelioma after cessation of asbestos exposure: a prospective cohort study of shipyard workers. Å. Sandén, B. Järvholm, S. Larsson, G. Thiringer.

ABSTRACT: A prospective cohort study of 3,893 shipyard workers, mainly exposed to chrysotile, indicated no increased risk of lung cancer 7–15 yrs after exposure to asbestos had ceased. The shipyard workers, however, had an increased risk of pleural mesotheliomas with 11 observed cases *versus* 1.5 expected.

An explanation for these observations may be that asbestos may have different carcinogenic mechanisms in causing lung cancer and mesothelioma. A non-increased risk of lung cancer some years after exposure to asbestos has stopped is in accordance with asbestos acting as a promotor. The high risk of mesothelioma, on the other hand, may indicate that asbestos acts as a complete carcinogen in developing this disease.

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Several studies have demonstrated an increased risk of lung cancer and mesothelioma in shipyard workers exposed to asbestos [1–6]. Shipyards used to be one of the major industries in Gothenburg, a city with about 440,000 inhabitants. In a case-reference study of shipyard workers in Gothenburg, we found a two-fold increase in mortality from lung cancer between 1960–1979 compared to the general male population [7]. This increase in lung cancer was probably caused by exposure to asbestos. However, almost all use of asbestos in the shipyards in Gothenburg ended in 1972.

Even if some of the above mentioned studies [1–3] included some persons whose exposure to asbestos had come to an end, their analyses had not specifically addressed these questions. The objective of this study was to investigate cancer morbidity of lung cancer and malignant mesothelioma in shipyard workers some years after exposure to asbestos had ceased.

Subjects

The shipyards in Gothenburg had no registration of workers previously exposed to asbestos. Therefore, in 1976, every worker who considered himself to have been exposed to asbestos was requested to put his name on a list. Strong union support for having all asbestos exposed workers registered contributed to good compliance. These workers were invited to a health check-up which was subsidized by the government and free of charge.

Three thousand eight hundred and ninety nine shipyard workers participated in the health check-up. Only six of these were women and, because they were few, they were excluded from the analysis. The cohort in this study therefore was the 3,893 men who participated in the health check programme at the shipyards between 1977 and 1979 (table 1).

Table 1. – Year of birth in shipyard workers (males)

Year of birth	n
1899–1909	33
1910–1919	636
1920–1929	1,089
1930–1939	849
1940–1949	793
1950–1960	493
Total	3,893

Methods

The study was a prospective cohort study where the morbidity of cancer in the shipyard workers was compared to the morbidity of the general male population of Gothenburg. The observation period for each man was the time between the health check and December 31, 1987, or the point of death or emigration (n=55) if this occurred before 1987. The 55 individuals who emigrated constituted the only losses during the follow-up period.

The cancer cases were found by linking the Swedish national identity number of each shipyard worker with the Swedish Cancer Register. The cancer morbidity rates for the male population of Gothenburg were taken from the Regional Tumour Register. Expected morbidity was calculated by multiplying the person-years during the observation period with the incidence rates, stratified for calendar year, age-class and gender [8]. All tumours have been classified according to the 7th revision of the International Classification of Diseases.

The health check programme included a self-administered questionnaire asking about smoking habits (table 2) and asbestos exposure. Every man underwent a chest radiograph (posterior-anterior and lateral views) and spirometry. The chest radiographs were read by the same physicians. Pleural plaques were classified according to THIRINGER *et al.* [9].

Table 2. – Smoking habits at the time of the health check

	n	%
Nonsmoker	832	21
Ex-smoker	1,219	31
Smokers	1,783	46
Unknown	59	2

The 95% confidence intervals of the ratios between observed and expected values have been described according to a Poisson distribution.

Exposure

For the early 1970s there are documented measurements from three Swedish shipyards of the exposure to asbestos fibres longer than 5 μm. In 44% of these measurements a fibre concentration of more than 2 fibres·cm^{-3} was observed [10]. The use of asbestos in Sweden was regulated in 1964 and the exposure was probably heavier before that time but we have no measurements from that period.

The use of asbestos at the shipyards had been documented by studying the purchases for each ship from 1950 until 1972, when its use ceased. After that time only a few men, who pulled down asbestos in ships at a repair yard, were exposed to asbestos. The rules for these jobs were strongly regulated and the exposure consequently very low. Between 1950 and 1972, 30–35 tons were used every year, mainly chrysotile. Amosite was used for spray insulation and cementing. Crocidolite was used in four naval ships during the 1950s. These insulation jobs were carried out by subcontractors not included in these studies.

Thus, workers in the present study were mainly exposed to chrysotile, but could have been indirectly exposed to amosite to some extent. In the 1950s, workers could have been indirectly exposed to crocidolite in the four naval ships. The shipyards produced about 8–10 ships annually and 4 naval ships in one decade was a small proportion of the total production.

To evaluate individual exposure, every man was asked to estimate his own asbestos exposure by answering a self-administered questionnaire. He reported when his asbestos exposure started and ceased. He also had to estimate the frequency of exposure. Each individual was also asked to estimate his total asbestos exposure according to a four stage spectrum (very low, low, heavy, very heavy).

Results

The total cancer morbidity in shipyard workers was somewhat less than in the reference population, 168 cases *versus* 196.4 expected (table 3).

Twenty two shipyard workers had developed lung cancer, which was slightly less than expected. Even men with a long interval since onset of exposure and heavy exposure to asbestos showed no increased risk of lung cancer compared to the male population of the same city (table 4). On the other hand, there was a highly increased risk of pleural mesothelioma, 11 cases

Table 3. – Observed and expected cancer morbidity between 1978 and 1987 in shipyard workers (n=3,893; 35,155.8 person-years)

Site	Number in ICD 7	Observed	Expected	95% CI of rate ratio
All	140–209	168	196.4	0.73–0.99
Lung	162.1	22	25.9	0.53–1.3
Pleural mesothelioma	162.2	11	1.5	3.7–13.1
Peritoneal mesothelioma	158	0		
Gastrointestinal tract	150–157	39	49.1	0.56–1.1
Stomach	151	7	10.1	0.28–1.4
Colon/rectum	153–154	17	20.5	0.48–1.3
Pancreas	157	9	5.9	0.70–2.9
Prostate	177	22	27.5	0.50–1.2
Kidney	180	6	12.4	0.18–1.1
Urinary bladder	181	10	15.9	0.30–1.2

ICD: International Classification of Diseases; 95% CI: 95% confidence interval.

versus 1.5 expected. There was no case of peritoneal mesothelioma. Four cases of pleural mesothelioma had estimated their exposure as very heavy, four cases as heavy and three cases as low. The latency periods between onset of asbestos exposure and occurrence of the mesothelioma ranged from 24–43 yrs.

Out of the 22 cases of lung cancer 16 were current smokers and 6 were ex-smokers at the time of the health check-up. No nonsmoker developed lung cancer during follow-up. Seven of the 11 cases with pleural mesotheliomas were current smokers. Two were ex-smokers and two were nonsmokers.

Table 4. – Observed and expected cancer morbidity between 1978 and 1987 in shipyard workers, (only men included) for whom at least 20 yrs had elapsed since the onset of asbestos exposure and with heavy or very heavy* exposure to asbestos (n=1,200; 9,248.6 person-years)

Site	Number in ICD 7	Observed	Expected	95% CI of rate ratio
All	140–209	70	76.3	0.72–1.2
Lung	162.1	11	10.2	0.54–1.9
Pleural mesothelioma	162.2	8	0.56	6.2–28.1
Gastrointestinal tract	150–157	18	19.7	0.54–1.44
Stomach	151	2	4.0	0.06–1.8
Colon/rectum	153–154	9	8.2	0.50–2.1
Pancreas	157	5	2.4	0.67–4.9
Prostate	177	8	11.6	0.30–1.4
Kidney	180	3	4.9	0.13–1.8
Urinary bladder	181	2	6.3	0.04–1.1

* according to each man's own opinion of his total exposure estimated in a four stage spectrum (very low, low, heavy, very heavy). ICD: International Classification of Diseases; 95% CI: 95% confidence interval.

There was no indication of an increased risk of gastrointestinal cancer. There were no indications of increased risks of lymphomas (4 observed *versus* 5.1 expected), laryngeal carcinomas (2 observed *versus* 3.9 expected) or kidney cancer (6 observed *versus* 12.4 expected).

In the group where at least 20 yrs had elapsed since onset of asbestos exposure at the health check-up (n=2,701), there were 21 cases of lung cancer *versus* 22.1 expected and 11 cases of mesothelioma *versus* 1.2 expected (95% confidence interval (CI) of relative risk 4.6–16.4). Thus, there was no increased incidence of lung cancer in men with at least 20 yrs latency time between start of asbestos exposure and start of observation period.

In men with pleural plaques and a time of at least 20 yrs from onset of asbestos exposure at the health check up (n=837), there were eight cases of lung cancer *versus* 9.9 expected and four malignant mesotheliomas *versus* 0.5 expected.

Discussion

This study indicates that shipyard workers in Sweden do not have any increased risk of lung cancer some years after exposure to asbestos has ceased. The number of cases are rather small and, therefore, a slightly elevated risk cannot be excluded (95% CI 0.5–1.3). The risk of mesothelioma was, however, increased.

Exposure and latency period

The increased incidence of lung cancer and malignant mesothelioma in our earlier study of shipyard workers in Gothenburg [7] indicated a high exposure to asbestos in the shipyards. Even a high prevalence of pleural plaques and asbestosis in the present study confirmed considerable asbestos exposure. In the group with at least 20 yrs latency time at the health check-up, the prevalence of pleural plaques was about 31% and the prevalence of asbestosis or suspect asbestosis about 2%.

Earlier studies have indicated that the latency period for lung cancer caused by asbestos is similar or shorter than for mesothelioma [2, 11–14]. The high incidence of mesothelioma in this study indicated that these shipyard workers had been exposed to asbestos and that sufficient time had elapsed to develop a cancer associated with asbestos.

We therefore believe that it is reasonable to conclude that the absence of an increased risk of developing lung cancer is not related to a low or absent exposure to asbestos, nor is too short a time since the onset of exposure.

Aspects of validity

The chest X-ray at health check-up and the questions about asbestos exposure were collected prospectively. Thus, there was no observer bias.

The only losses during the follow-up period were due to emigration. These men were included in the study until the moment of emigration. As they were

rather few it seems unlikely that this small loss could influence the result.

Comparing mortality in industrial workers with corresponding mortality in the general population usually leads to a slightly lower risk in industrial workers, *i.e.* the so called "healthy worker effect". Such a bias should be far less when studying morbidity in cancer. Forty six men who participated in the health check-up had previously diagnosed cancer of different types. This suggests that there was probably little "healthy worker" selection. The somewhat lower total morbidity in cancer in the shipyard workers (tables 3 and 4) may be just a random finding.

Smoking habits may be a confounder in estimating the risk of lung cancer. However, a comparison in 1985, of smoking habits in an age-stratified random sample of the cohort and the male population of the same city indicated similar smoking habits in the two groups [15]. There were 31% current smokers in both groups, 42% ex-smokers in shipyard workers and 35% in male inhabitants of Gothenburg. Thus, a non-increased risk of lung cancer in shipyard workers could not be explained by fewer smokers in this group.

Lung cancer

Several investigators have found an increased risk of lung cancer in shipyard workers exposed to asbestos. Most of these studies [1–6] with a relative risk of lung cancer between 1.4–2.2 were in agreement with the observation in our earlier study [7]. Some investigators [16, 17] have found a relative risk of 1.2 but even these studies indicated a higher risk of lung cancer than our present study.

A non-increased risk of lung cancer in the present study may be due to low exposure, low smoking habits or too short a latency period. As discussed above, the smoking habits could not explain the non-increased risk. Low exposure is also an improbable explanation as measurements in the early 1970s showed high concentrations of asbestos fibres and there was a high prevalence of pleural plaques and asbestosis, together with a high incidence of mesotheliomas, which all indicate a considerable exposure to asbestos. An analysis restricted to men with latency periods of more than 20 yrs at the health check-up does not indicate an increased risk. All men in that analysis started their exposure before the regulation of asbestos exposure in 1964.

None of the other studies [1–6, 16, 17] have focused on the risk after discontinued asbestos exposure. In this study exposure ceased some years before the observation period. This fact may explain the lower risk of lung cancer in our study compared to the findings in other studies of shipyard workers.

WALKER [18] discussed the possibility of a decline in the relative risk of lung cancer some time after cessation of asbestos exposure. He pointed out that a decline in relative risk for lung cancer after the cessation of asbestos exposure is analogous to the reduction in relative risk of lung cancer after the termination of cigarette smoking. This question was also discussed by DOLL and PETO [11]. They were of the opinion that the assumption that the relative risk will remain constant after discontinued exposure was open to serious doubt, especially for chrysotile.

Studies of the mechanisms of asbestos carcinogenesis indicate that asbestos acts as a classic tumour promotor in developing bronchogenic carcinoma [19, 20]. Elimination of a promotor ought to reduce the cancer risk some time after exposure has stopped. Asbestos fibres are retained in the lung tissue for a long time. However, chrysotile is cleared faster from the lungs than amphiboles [21]. The risk of lung cancer after stopping exposure may be different in individuals exposed to chrysotile and to amphiboles. Our study included subjects mainly exposed to chrysotile, and the findings may not be valid for persons exposed to amphiboles.

Mesothelioma

The observation in this study of a high risk of mesothelioma and a long latency period for the disease to occur was in agreement with the findings in several other studies of shipyard workers [2, 5, 12, 14, 16]. The average latency period in the present study was 33 yrs. Similar or even larger latency periods have been reported [5, 11, 12]. Thus, persons with short latency intervals contribute little information about the risk of mesotheliomas.

The incidence of pleural mesotheliomas in men with 20+ yrs latency period in the present study was 0.54 per 1,000 person-years. No peritoneal mesothelioma was found. In a study of Swedish asbestos cement workers the corresponding incidence was 0.59 per 1,000 [22]. Even these men were mainly exposed to chrysotile and all cases were pleural.

PETO *et al.* [23] observed an incidence of pleural mesotheliomas of 0.42 per 1,000 person-years in textile workers with 20+ yrs from onset of asbestos exposure. They were mainly exposed to chrysotile, but also to some crocidolite.

In a study of American insulation workers SELIKOFF *et al.* [24] observed an incidence of 0.79 per 1,000 person-years for pleural mesotheliomas and 1.41 per 1,000 for peritoneal mesotheliomas when using best evidence (autopsy, surgical, clinical) but an incidence of 0.3 per 1,000 for pleural mesotheliomas and 0.31 per 1,000 for peritoneal when using death certificate information only. There was an excess risk of lung cancer in the studies of PETO *et al.* [23] and SELIKOFF *et al.* [24], but in the study of Swedish asbestos cement workers there was no such excess risk of lung cancer, in accordance with the observation in our study.

Ending exposure to asbestos evidently did not reduce the risk of mesothelioma. In men exposed to amphiboles the fibres are retained in the tissue for a long time and asbestos may, therefore, develop

mesothelioma even after exposure has ceased. In men mainly exposed to chrysotile, however, the explanation is probably different; perhaps that asbestos appears to be a complete carcinogen in causing mesothelioma, possessing both initiating and promoting properties [25, 26].

Other sites of cancer

There was no increased risk of gastrointestinal cancers in this study, which is in agreement with some other studies of workers exposed to asbestos [27]. Some studies have indicated an increased risk of kidney cancer [28], lymphomas [29] and laryngeal carcinoma [30] in workers exposed to asbestos. The morbidity of cancer in these sites was, however, not increased in our study, but the study has a low power in detecting an increased risk in these sites.

There was a numerical but non-significant increase of pancreatic cancer. This may be a random finding or there might be misdiagnosed peritoneal mesotheliomas [13].

Conclusions

This study indicates that shipyard workers exposed to mainly chrysotile had no increased risk of lung cancer some years after exposure to asbestos had ceased but a highly increased risk of mesothelioma. This is probably due to differences in the carcinogenic mechanisms. Asbestos seems to act as a promotor in developing lung cancer but as a complete carcinogen in developing mesothelioma.

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