Quantitative importance of asbestos as a cause of lung cancer in a Swedish industrial city: a case-referent study

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Quantitative importance of asbestos as a cause of lung cancer in a Swedish industrial city: a case-referent study. B. Järvholm, S. Larsson, S. Hagberg, S. Olling, W. Ryd, K. Torén. ©ERS Journals Ltd 1993.
ABSTRACT: We wanted to assess the quantitative importance of asbestos as a cause of lung cancer.

In a case-referent study, the exposure to asbestos, tobacco smoke and some other occupational exposures were compared between 147 cases of lung cancer (100 men, 47 women), 111 hospital referents, and 109 population referents, all below the age of 75 yrs and living in an industrial city.

The attributable risk of lung cancer due to asbestos exposure was 16% in men (95% confidence interval 1–31%). No woman had occupational exposure to asbestos.

We conclude that in the mid 1980's tobacco smoking was the major attributable risk, being 95% for men and 78% for women, but that in men asbestos was an appreciable contributing factor in the general population of a Swedish industrial city.
Eur Respir J., 1993, 6, 1271–1275.

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Smoking is the major preventable factor for lung cancer in the general population in Western countries. In some groups, occupational exposures are also important preventable factors. The quantitative importance of occupational factors as a cause of lung cancer has been estimated as 9 and 8% in the north and southeast of Sweden, respectively, in case-referent studies [1, 2]. Neither of these investigations included any large city or tried to estimate the importance of single occupational factors. The quantitative importance of a certain factor depends on the size of the relative risk and the size of the exposed population.

Göteborg is an industrial city in western Sweden, with approximately 440,000 inhabitants. In the past, shipbuilding was a major industry, with about 17,000 employees in the early 1970s. Today, the largest industry is automobile manufacturing. There are also other engineering industries, chemical industries, refineries, *etc.* Asbestos, a well known risk for lung cancer, was a rather common occupational exposure, especially in the shipyard industry.

The objective of this study was to estimate the quantitative importance of asbestos exposure as a cause of lung cancer in the general population of this city in the mid 1980s. It is a case-referent study, including both male and female patients at a chest clinic. The study was restricted to patients up to 75 yrs of age.

Subjects

Cases

The investigation was designed as a case-referent study, where the information about exposure was collected from interviews with the persons present. The cases were patients with lung cancer (ICD 9,162) at Renströmska Hospital, Göteborg. This is the only chest clinic in the city. Both in-patients and out-patients have been included. The study includes men and women living in Göteborg or its surroundings (the municipalities of Göteborg, Kungälv, Partille and Mölndal).

The study began in February 1983 and ended in October 1984. Through regular visits to the out-patient units and departments at the hospital, we tried to find all patients who were referred to the hospital with a suspicion of lung cancer. We only interviewed new cases, *i.e.* cases where the diagnosis was not yet established. Only patients of 75 yrs and younger were included (table 1). Some possible cases died before the interview, or were in too poor a condition for interview.

Hospital referents

The examination of some subjects who were referred to the hospital owing to a suspicion of lung cancer failed

Table 1. – Age and gender in cases and referents

Age yrs	Cases M	Cases F	Popn. referents M	Popn. referents F	Hospital referents M	Hospital referents F	Excluded referents* M	Excluded referents* F
20–29	0	0	0	0	1	0	0	0
30–39	1	0	3	1	5	3	2	0
40–49	5	3	5	3	7	2	8	1
50–59	23	4	13	6	17	13	11	1
60–69	51	25	29	18	29	22	12	4
70–75	20	15	23	8	13	9	5	0
Total	100	47	73	36	72	49	38	6
Mean age yrs	63	65	63	63	59	61	57	59

*: excluded hospital referents. M: male; F: female. Popn: population.

to demonstrate lung cancer. These persons were included as "referents". However, some occupational groups in the city are being screened, because of asbestos exposure. Such screenings included chest radiographs. Because of suspected pathological findings in the chest radiographs, such persons can be expected to be referred to the hospital more often. Among the hospital referents, we therefore excluded patients who had been referred to the hospital from an occupational health centre or due to findings in health screening. We also excluded patients who had diseases associated with asbestos, *i.e.* pleural plaques, pleural fibrosis, asbestosis or pleurisy due to asbestos. Forty four referents were thus excluded, leaving 121 hospital referents (table 1).

Population referents

From a population register, we randomly selected 95 men and 54 women from the same municipalities as the cases. At the time of selection, we did not know exactly how many cases of cancer there would be, but tried to select as many referents from the population as the number of cancer cases. These referents were randomly selected in age classes (10 yr age classes) in order to have similar numbers of referents in each age class as the number of cancer cases. Twenty seven percent of the selected population referents did not come to the interview. Twelve men and 12 women preferred not to take part; two men and two women did not reply to the invitation; six persons had moved to other areas; and six persons had died between the time of selection and the time of interview. Referents were interviewed up to about 2 yrs after the selection.

Methods

All patients and referents were interviewed by one of three trained assistants. The questionnaire included detailed questions about smoking habits, asbestos exposure, and several questions about different occupational exposures. Most questions were yes/no questions, and if the answer was "yes" the patient was asked

to describe the exposure in more detail. There was also an open question about occupational career. Most population referents were, for practical reasons, interviewed by one of the interviewers. As all interviewers were trained and the questions were mostly yes/no, we think this procedure is unlikely to introduce any observer bias. The questionnaire contained a question about where the persons had lived (only permanent addresses for more than 3 yrs), and type of house (single family, apartment house, *etc*). These answers were similar between cases, hospital and population referents, respectively, making an observer bias improbable. The median number of addresses for all groups were 3.5; and 92, 93 and 95% of male cases, hospital and population referents, respectively, had six or fewer addresses.

The histological classification of all cases was re-examined by a pathologist (SO). Cytological specimens were also reviewed by a cytologist (WR). In 24 cases, the diagnoses were based on cytological examination only. The histological classification indicated a majority of squamous cell carcinomas in men (47%), and a similar number of adenocarcinomas and squamous cell carcinomas in women (30% and 34%, respectively). Small cell carcinomas constituted approximately 20% in both men and women.

A trained occupational hygienist (SH) classified all persons according to cumulative asbestos exposure into four categories (>25 fibre-years·ml⁻¹, 1–24 fibre-years·ml⁻¹, 0.05–0.9 fibre-years·ml⁻¹ and <0.05 fibre-years·ml⁻¹). The classification was performed without knowledge about whether or not the questionnaire came from a case or a referent, and was based on the persons occupational history and specific questions about exposure to asbestos (duration, intensity, type of jobs). The times of the classification of questionnaires were randomly distributed between cases and referents.

Attributable risks stratified for possible confounders and their 95% confidence intervals (CI) were calculated, according to WHITTEMORE [3]. The odds ratios (OR) for stratified data were estimated according to MANTEL and HAENSZEL [4]. The confidence intervals of odds ratios were estimated using the test-based method [5].

Results

Tobacco smoking

Only one man and six women were life-long non-smokers. As expected, the risk of lung cancer was highly dependent on exposure to tobacco smoke (table 2). Even in the categories ex-smokers and current smokers, the cases had heavier smoking habits than the referents. The attributable risk for ever being a smoker is 95% (95% CI 0.91–0.98) for men, and 78% (95% CI 0.69–0.87) for women.

As the number of nonsmokers with lung cancer is small, the power to estimate the risk of passive smoking is low. Three life-long nonsmoking female cases and 21 female referents were classified as exposed to environmental tobacco smoke (OR=1.0, 95% CI 0.1–3.8).

Occupational exposure

Occupational asbestos exposure had only occurred among the men. All women were classified in the lowest category of asbestos exposure (<0.05 fibre-years·ml⁻¹). The male cases had been exposed to asbestos somewhat more often than the referents, but the difference was not statistically significant (table 3). The OR, adjusted for smoking habits, for a cumulative dose of >1 fibre-years·ml⁻¹ was 1.7 (95% CI 0.6–5.1) including both population controls and hospital controls and 1.8 (95% CI 0.4–7.5) including only population controls. The corresponding figures for a cumulative dose of >0.05 fibre-years·ml⁻¹ was 1.6 (95% CI 0.9–2.8) and 1.6 (95% CI 0.8–3.3), respectively.

Twenty three of the cases had worked at shipyards. The most common type of work with exposure to asbestos was insulating with asbestos, which was reported by 15 cases and 11 population referents. Only one male case was a life-long nonsmoker. He was classified as exposed to 0.05–0.9 fibre-years·ml⁻¹ of asbestos.

Eight women with lung cancer answered that they had indirect asbestos exposure at home, while the corresponding figures for population and hospital referents

Table 3. – Estimated cumulative dose of asbestos in cases and referents, men only

Dose*	OR**	Cases	Population referents	Hospital referents	Excluded referents
<0.05	1.0	57	47	52	11
0.05–0.9	1.6 (0.9–2.8)	34	22	15	18
1.0–24.9	1.4 (0.5–3.8)	7	4	5	8
≥25.0	-	2	0	0	1

*: fibre-years·ml⁻¹; **: odds ratio (OR) compared with exposure to <0.05 fibre-years·ml⁻¹, adjusted for smoking habits, and 95% confidence interval in parenthesis.

were 19 and 14, respectively. Thus, there was no indication that passive exposure to asbestos at home was an important cause of lung cancer in women.

The attributable risk of lung cancer due to asbestos exposure adjusted to smoking habits (a cumulative exposure of >0.05 fibre-years·ml⁻¹) is 16% (95% CI -0.1–0.43) if only population referents are considered, and 16% (95% CI 0.01–0.31) if all referents are considered.

The histological category of lung cancer did not reveal any obvious pattern according to asbestos exposure.

Table 4. – Some occupational exposures in male cases and referents (hospital and population referents merged)

Exposure/industry	Cases/referents	OR*
Chemical industry	2/9	0.31 (0.1–1.4)
Metal refining	2/0	
Chromates/chromium plating	1/1	
Welding in stainless steel	4/7	0.82 (0.4–1.7)
Nickel	0/2	
Cadmium	1/2	
Arsenic	2/4	
Oil mist	10/6	2.6 (1.2–5.5)
Wood dust	5/11	0.64 (0.3–1.5)
Painting	7/8	1.3 (0.6–2.8)

Odds ratios are only calculated when total number of cases + referents ≥10. *: odds ratio and 95% confidence interval in parenthesis.

Table 2. – Smoking habits in cases and referents (Ref), population referents only

Smoking habits	Male Cases/Ref	OR*	Female Cases/Ref	OR*
Nonsmokers	1/16	1.0	6/21	1.0
Ex-smoker	26/28	15 (3–81)	10/8	4.4 (1.2–16)
Smokers	73/29	40 (10–164)	31/7	16 (5–48)
Total consumption of tobacco kg				
≤99	2/7	4.6 (0.4–53)	3/3	3.5 (0.6–21)
100–199	22/14	25 (5–136)	11/3	13 (3–55)
200–299	22/6	59 (11–323)	12/1	42 (7–249)
300–399	13/1	208 (23–1870)	3/0	-
≥400	14/1	224 (25–1978)	2/0	-

*: odds ratio (OR) compared to nonsmokers, and 95% confidence interval in parenthesis.

However, the number of cases in each category was rather small.

Oil mist, including aerosols of cutting fluids, was the only occupational exposure which indicated a statistically significant risk in this study (OR=2.6, 95% CI 1.2–5.5). Six cases and two referents reported exposure to aerosols of cutting fluids. Most exposures asked about were confirmed by only a few (table 4). The corresponding figures for women are not shown, as only three women reported any such exposure (one case and two referents).

Discussion

This study shows, not surprisingly, that the major preventive factor for lung cancer in an industrial Swedish city is tobacco smoking. However, the results indicate that efforts to reduce asbestos exposure may reduce the incidence among men. We first discuss some methodological issues and then practical implications for prevention.

Methodological issues

It is often argued that a person with severe disease is more motivated to remember exposure than randomly selected healthy controls. However, in this study, we also interviewed hospital controls, who were under examination for possible lung cancer. The psychological stress to remember was, therefore, similar in these referents and cases. The answers to questions about occupational exposure among hospital and population referents were similar, and it is, therefore, reasonable to assume that information bias is of little importance in this study. The slightly larger OR for asbestos exposure when only population referents were considered (1.8 vs 1.7) is easily understood, as asbestos exposure was somewhat reduced among hospital referents according to the exclusion criteria (see above).

The OR for an estimated exposure to asbestos of 1.0–24.9 fibre-years·ml^{-1} was 1.4 (95% CI 0.5– 3.8) and the corresponding OR for 0.05–0.9 fibre-years·ml^{-1} was 1.6 (95% CI 0.9–2.8). These risks are somewhat larger than the increase of 0.01 per fibre-years·ml^{-1} of the relative risk, as estimated by DOLL and PETO [6]. However, the OR are based on a rather limited number of cases, and the CI are wide, including the estimate by DOLL and PETO [6].

The cases in this sample consist of patients at a certain hospital who were available for interview. A comparison with the Cancer Register indicated that about 50% of all incident cases in the total city during the observation period were interviewed by us. It is reasonable to assume that those who were not interviewed either had a very fulminant disease with a very short time between onset of symptoms and death, or were discovered at autopsy. Persons with very severe disease may have been judged as being beyond curative therapy and were, therefore, not referred to the lung clinic.

A comparison between the histological diagnoses in the Cancer Register and our material support such a hypothesis, since small cell carcinoma were somewhat more common in the Cancer Register. This finding may have influenced the estimation of the quantitative importance of different causative factors, if these factors are more or less prone to cause different histological types. There is no certain histological type that is very much more strongly associated with asbestos exposure. It has sometimes been discussed that asbestos may more often cause adenocarcinomas. If this is true, we may somewhat overestimate the quantitative importance of asbestos in the general population. However, the bias should be rather small, as the frequency of adenocarcinomas in men were rather similar (17 and 15% in our material and Cancer Register, respectively).

Occupational factors

The results indicate that asbestos exposure has importance for the occurrence of lung cancer in men but not in women. The incidence of pleural mesothelioma was 15 and 5 per million and year in this area for men and women, respectively. The difference between men and women in their incidence of mesothelioma is in accordance with our observation of an association between asbestos exposures and lung cancer in male cases only. However, it is hard to estimate from the incidence of the mesothelioma the importance of asbestos as a cause of lung cancer, as the dose response relationships are different [6]. The results indicate that the elimination of asbestos may reduce the incidence of lung cancer in this city by about 15% among men. However, this figure is somewhat uncertain, owing to the limited material and the 95% confidence limit goes from a negligible (0.01%) to a considerable (0.31%) risk. A figure of 15% may be regarded as small and unimportant as compared with the aetiological fraction of tobacco smoking. However, this figure is of similar size to the proportion of curable cases of lung cancer in the general population. Due to strict regulations, exposure to asbestos is almost totally eliminated in Sweden today. The importance of a preventable factor is not only dependent on its quantitative size but also on the possibilities of prevention. In the case of asbestos, it can thus be concluded that the possibilities to reduce exposure, i.e. primary prevention, have been excellent. Prevention of asbestos exposure in certain occupational groups, e.g. shipyard workers and insulators, may also have far more relative importance. There are no other estimations of the relative importance of asbestos as a cause of lung cancer in Sweden. DOLL and PETO [7] estimated that asbestos caused about 5% of all "present-day" lung cancer in the US.

DAMBER and LARSSON [1] estimated that 9% of all male lung cancer in northern Sweden was due to occupational factors, and DAVE et al. [2] found a corresponding figure of 8% in southeastern Sweden, including both men and women. Our results indicate a somewhat higher attributable risk for occupational factors in men. This may easily be understood, as Göteborg has had a major

shipyard industry. Studies from highly industrialized areas in Porsgrunn, Norway and Lombardy, Italy indicated somewhat higher estimates of the proportion of lung cancer attributable to occupation, i.e. 30–40% [8, 9]. In different areas of the USA, VINEIS et al. [10] estimated that 3–17% of lung cancer in males was due to occupation.

Our results indicated that oil mist may be a cause of lung cancer. However, this finding is based on a small number of cases, and studies in the engineering industries have not indicated an increased risk of lung cancer due to exposure to aerosols of cutting fluids [11–15].

Our study is too small to estimate the aetiological fraction of other known occupational carcinogens as a cause of lung cancer in Göteborg. However, as such exposure seem to be rare, even if the risk is high, the overall importance in the general population is small. This must not be taken as an argument against prevention, as a decrease of exposure may be of great importance in certain, occupational groups.

Tobacco smoking

This study certainly shows that if there was no smoking of tobacco, lung cancer would be a very rare disease in Göteborg. The number of life-long nonsmokers is very small in this group of patients. We think our information about tobacco smoking is reliable, as it is taken by interview of the patient himself. A close relative may wrongly classify ex-smokers as nonsmokers in an interview by questionnaire. We do not think that people overestimate their own smoking habits.

There was one case of lung cancer among nonsmoking men, and six cases among nonsmoking women. Nonsmokers constituted 22% of the male population referents, and the corresponding figure for women was 58%. As the number of men and women is similar in these ages, we would have expected about 2.6 nonsmoking women among the female cases, if they had the same incidence as men. This difference may be just a random finding (p=0.1, Poisson test, two-tailed). The women may also have underreported their smoking habits, as smoking may be regarded as a non-acceptable habit among women of this age.

Conclusions

The attributable risk of asbestos exposure in the general male population of a highly industrialized Swedish city seems to be of the order of 15% (95% CI 1–31%) in men in the mid 1980s. The highest attributable risk by far was for tobacco smoking, i.e. 95% for men and 78% for women.

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