Incidence of lung cancer by histological type among asbestos cement workers in Denmark

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Abstract

Objective—A significant twofold increased risk of lung cancer was found among 8000 men employed in the Danish asbestos cement industry between 1928 and 1984. The histological pattern of 104 lung cancer cases was studied with the aim of evaluating a relation between specific morphological types, duration of employment, and time since first employment.

Methods—Age, sex, and calendar time specific incidence of morphological subtypes of lung cancer (adenocarcinoma, squamous cell carcinoma, anaplastic carcinoma, and unspecified malignant tumour) for all Danish men were computed from 1943 to 1984, from data routinely collected by the Danish Cancer Registry. Person-years of observation were counted from 15 years after the date of first employment until date of diagnosis of cancer, death, emigration, or the end of follow up on 31 December 1984. Expected numbers of cases were computed by applying person-years at risk to the appropriate incidence rates. Observed numbers were distributed accordingly and the relative risk calculated.

Results—The relative risk for adenocarcinoma was 3.31 (observed (O) 24, expected (E) 7.26), for squamous cell carcinoma 1.67 (O, 37, E, 22.12), for anaplastic carcinoma 1.58 (O, 23, E, 14.53), and for unspecified malignant tumour 1.57 (O, 18, E, 11.46). An increased risk by duration of employment and time since first employment was most pronounced for adenocarcinoma.

Conclusion—The link between adenocarcinoma and asbestos was confirmed in this, the first study of risk of lung cancer by histological

category based on incident cancer cases for a whole population during a 50 year period.

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Lung cancer is the most common cancer for men in Denmark with more than 2000 new cases occurring annually.¹ Among asbestos workers lung cancer is the most frequent single cause of death.² Selikoff *et al* found in their study on mortality among 18 000 insulation workers in the United States that one out of five deaths was caused by lung cancer.³ The histopathological pattern of lung cancer among persons exposed to asbestos has been reported in several studies.⁴⁻¹² A preponderance of adenocarcinomas is present in some of these studies.⁴⁻⁸ The relative frequency of cell types seems, however, to depend on the source of pathological material, as shown by Whitwell *et al*.⁸ The question remains, therefore, whether there was, in fact, a higher proportion of adenocarcinomas or whether this high frequency was due to a bias in the material.

Thus we studied the incidence of lung cancer by histological type in a cohort of men previously employed in the asbestos cement industry in Denmark.

Materials and methods

In Denmark, asbestos cement products were manufactured by one factory only, Dansk Eternit in Aalborg.¹³ Production began in 1928 and accounted for 90% of the total amount of imported raw asbestos into Denmark.

Chrysotile asbestos was the only type of fibre used until 1946 when amosite was introduced. Small amounts of crocidolite were also used between 1952 and 1968.

Measurements of atmospheric asbestos particles carried out in 1948 and 1957 showed that the highest concentration of particles occurred during feeding the mill and the forming vessel. The Danish National Institute of Occupational Health has estimated that the concentration measured in fibres (f) per ml in 1948 varied between 50 and 800 f/ml and in 1957 between 10 and 100 f/ml (T Schneider, personal communication). In 1973 41% of the exposure measurements were recorded as being above 2.0 f/ml.

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Information on all persons ever employed between 1928 and 1984 was extracted from the personnel files of the company. Over 99% of the employees were traced, giving a total of 7996 men and 584 women.

Information about death, causes of death, and cancer cases was extracted from municipality population registers, the Danish Cause of Death Register, and the Danish Cancer Register. The Danish Cancer Register contains information on all incident cancer cases diagnosed in Denmark since 1943. Between 1943 and 1977 cases of cancer were coded according to a modified version of ICD-7¹⁴ in which a distinction was made between histologically verified subgroups of lung cancer. Since 1978 all cancer cases have been coded according to ICD-0.^{15,16}

Age, sex, and calendar year specific incidence rates by morphological subtype of lung cancer for all Danish males were computed. The following classification was used: unspecified malignant tumour, adenocarcinoma, squamous cell carcinoma, anaplastic carcinoma (including large cell and oat cell carcinomas), and other specified types.

Person-years were calculated from 15 years from the date of first employment until the date of cancer diagnosis, death, emigration, or the end of follow up on 31 December 1984. The expected number of cases was computed by applying person-years at risk to the appropriate incidence rates. Observed numbers were distributed accordingly, and the relative risks were estimated as the observed divided by the expected numbers. Two sided 95% confidence intervals (95% CIs) for the relative risks were calculated using Byars approximation for the χ^2 distribution.¹⁷

Results

Between 1943 and 1984 a total number of 162 cases of lung cancer were found among men employed at Dansk Eternit Fabrik during the period from 1928 to 1984.¹³ Table 1 shows the lung cancer cases by histological group. Squamous cell carcinoma was the most common cell type with 62 cases, then anaplastic carcinoma and adenocarcinoma with 38 and 32 cases respectively.

Three cases of lung cancer were excluded from further analysis because they belonged to a subgroup of 46 men with irregular working periods. Fifty five of the remaining lung cancer cases were diagnosed within 15 years of the date of first employment and were consequently also excluded from the analysis.

Table 2 presents the histological types of lung cancer seen among 104 men employed at the Dansk Eternit Fabrik after a latency of 15 years from the date of first employment. The relative risk was significantly increased for adenocarcinoma (O 24, O/E = 3.31; 95%CI 2.12-4.92), and for squamous cell carcinoma (O 37, O/E = 1.67; 95%CI 1.18-2.31). For anaplastic carcinoma (O/E = 1.58), and for

Table 1 Cases of lung cancer by histological type among men employed in the asbestos cement industry in Denmark 1928-84 and followed up from 1943 to 1984

ICD-7	Histological type	No (%)
162-0, 1	Unspecified malignant tumour	25 (15)
162-4	Adenocarcinoma	32 (20)
162-5	Squamous cell carcinoma	62 (38)
162-6	Anaplastic carcinoma	38 (24)
162-7	Other specified	5 (3)
162-0-7	All lung cancer cases	162 (100)

Table 2 Incidence of lung cancer by histological type among men in the asbestos cement industry in Denmark, with 15 years latency

Histological type	ICD-7	O	O/E	95% CI
Unspecified malignant tumour	162-0, 1	18	1.57	0.93-2.48
Adenocarcinoma	162-4	24	3.31	2.12-4.92
Squamous cell carcinoma	162-5	37	1.67	1.18-2.31
Anaplastic carcinoma	162-6	23	1.58	1.00-2.38
Other specified	162-7	2	1.04	0.12-3.76
All lung cancer cases	162-0-7	104	1.82	1.48-2.20

histologically unspecified malignant tumour (O/E = 1.57) the O/E ratios were at the borderline of statistical significance.

Incidence of lung cancer was correlated with three durations of employment: less than one year, one to four years, and five years or more. Figure 1 and table 3 present the results. The relative risks were 2.18, 0.96, and 1.57 for squamous cell carcinoma and 1.56, 0.98, and 1.75 for anaplastic carcinoma in the respective three periods. The relative risk for adenocarcinomas was 2.32 among persons employed for less than one year. This risk increased to 3.60 for persons

Figure 1 Incidence of lung cancer by histological type and duration of employment.

Table 3 Incidence of lung cancer by histological type and duration of employment among men employed in the asbestos cement industry in Denmark, with 15 years latency

Histology	Duration of employment (y)								
	<1			1-4			≥5		
	O	E	O/E (95% CI)	O	E	O/E (95% CI)	O	E	O/E (95% CI)
Unspecified malignant tumour	4	3.61	1.11 (0.30-2.84)	2	1.57	1.27 (0.14-4.60)	12	6.28	1.91 (0.99-3.34)
Adenocarcinoma	16	2.58	2.32 (0.85-5.06)	4	1.11	3.60 (0.97-9.23)	14	3.57	3.92 (2.14-6.58)
Squamous cell carcinoma	15	6.87	2.18 (1.22-3.60)	3	3.13	0.96 (0.19-2.88)	19	12.12	1.57 (0.94-2.45)
Anaplastic carcinoma	7	4.49	1.56 (0.62-3.21)	2	2.05	0.98 (0.11-3.52)	14	7.99	1.75 (0.96-2.94)
Other specified	2	0.39	5.08 (0.58-18.52)	0	0.19	—	0	1.34	—
All lung cancer	34	17.94	1.89 (1.31-2.65)	11	8.05	1.37 (0.68-2.44)	59	31.31	1.88 (1.43-2.43)

Table 4 Incidence of lung cancer by histological type and time since first exposure among men employed in the asbestos cement industry

Histology	Time since first exposure (y)								
	15-24			25-34			≥34		
	O	E	O/E (95% CI)	O	E	O/E (95% CI)	O	E	O/E (95% CI)
Unspecified malignant tumour	6	5.15	1.17 (0.43-2.54)	9	3.44	2.62 (1.19-4.97)	3	2.87	1.05 (0.21-3.05)
Adenocarcinoma	7	3.67	1.91 (0.76-3.93)	10	2.12	4.72 (2.26-8.68)	7	1.46	4.79 (1.92-9.88)
Squamous cell carcinoma	18	10.46	1.72 (1.02-2.72)	11	6.88	1.60 (0.80-2.86)	8	4.80	1.67 (0.72-3.28)
Anaplastic carcinoma	9	7.96	1.27 (0.58-2.42)	11	4.48	2.46 (1.22-4.39)	3	2.98	1.01 (0.20-2.94)
Other specified	2	0.98	2.04 (0.23-7.37)	0	0.65	—	0	0.29	—
All lung cancer	42	27.34	1.54 (1.11-2.08)	41	17.59	2.33 (1.67-3.16)	21	12.40	1.69 (1.05-2.59)

employed from one to four years and to 3.92 for persons employed five years or more.

The relative risks for the histological types of lung cancer studied here were also correlated with time since first employment (table 4). The cohort was divided into three groups according to time since first exposure: these were 15 to 24 years, 25 to 34 years, and 35 or more. For anaplastic carcinoma the relative

risks increased from 1.27 for the period 15 to 24 years since onset of exposure to 2.46 for the period 25 to 34 years since onset. The relative risk of anaplastic carcinoma decreased to 1.01 at 35 years or more after first employment. For adenocarcinomas the corresponding relative risks were 1.91, 4.72, and 4.79 respectively, for the periods 15 to 24, 25 to 34, and 35 or more years since first employment (fig 2).

Figure 2 Incidence of lung cancer by histological type and time since first exposure.

Discussion

Our study, based on incidence data for cases of lung cancer diagnosed in Denmark since 1943, shows that the relative risk of adenocarcinoma of the lung among asbestos workers is two or more times higher than the

Figure 3 Frequency of necropsy among men in Denmark and in the city of Aalborg.

relative risk of squamous cell carcinoma and anaplastic carcinoma of the lung. An increasing relative risk by duration of employment and time since first employment was found only for adenocarcinoma. Our results thus agree with the epidemiological studies of Hueper *et al*, Hourihane and McCaughey, Kannerstein and Churg, Warnock and Churg, and Whitwell *et al*,⁴⁻⁸ and with the experimental study of Davies *et al*.¹⁸

Whitwell *et al* have shown that histopathological diagnoses, based on bronchial biopsy specimens, give a higher frequency of squamous and small cell carcinoma and a corresponding lower frequency of adenocarcinoma than necropsy series. The reason for these differences is that the squamous and small cell carcinomas generally occur in the larger bronchi accessible to biopsy, whereas the adenocarcinomas are usually in peripheral locations. Necropsy series, on the other hand, give a higher proportion of adenocarcinomas that are more often placed peripherally.⁸ The reason could be that necropsies are more frequently made when the histological diagnosis is not known from biopsies, and these cases will by definition include a higher proportion of adenocarcinomas.

To evaluate a possible bias due to different sources of pathological material in Aalborg and in Denmark as a whole, we investigated whether the frequency of necropsy was higher in Aalborg than in the rest of the country. It was not (fig 3).

Smoking is assumed to be the predominant cause of lung cancer and accounts for 80-90% of all cases.¹⁹ Unfortunately, smoking habits have never been studied among the employees at Dansk Eternit A/S. A cross sectional study on smoking habits among cement workers in Aalborg in 1973 showed that the prevalence of present and former smokers was 95%, and 92% among men in Aalborg in general.²⁰

The relation between squamous cell and small cell carcinomas of the lung and cigarette smoking is well established,²¹ but the relation between adenocarcinomas and cigarette smoking is still under discussion.²² Doll and Hill stated in their study of British doctors that there was no marked association between smoking and risk of adenocarcinoma of the lung,²³ and Kreyberg made the assumption that adenocarcinomas have little or no causal relation with smoking.²¹ By contrast, Weiss and co-workers found that well differentiated squamous cell carcinoma, small cell carcinoma, and adenocarcinoma of the lung all displayed a dose response relation with smoking,²⁴ as also shown by Lubin and Blot, although the risk for adenocarcinomas was at a reduced level.²⁵

The interaction between tobacco smoking and exposure to asbestos as a cause of lung cancer is controversial and is often stated as multiplicative with reference to the study of Selikoff *et al* in 1968.²⁶ Steenland and Thun²⁷ and Sarracci²⁸ have reviewed

all the asbestos studies with information about smoking habits to determine whether smoking modifies the effect of asbestos, and they concluded that the interaction varies between additivity and multiplicativity. None of the studies reviewed included data on tobacco smoking and exposure to asbestos in relation to histological type of lung cancer. The results in our study indicate that the relation between exposure to asbestos and the risk of adenocarcinoma of the lung is different from the relation between exposure to asbestos and the risk of squamous cell carcinoma and anaplastic carcinoma of the lung.

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