RISK FACTORS ASSOCIATED WITH ASBESTOS-RELATED DISEASES: RESULTS OF THE ASBESTOS SURVEILLANCE PROGRAMME AACHEN

***Khaled Khatab,[1] Michael K. Felten,[2] Nagianga B. Kandala,[3] Gebrenegus Ghilagaber,[4] Anil Gumber,[1] Thomas Kraus[2]**

1. Centre of Health and Social Care Research, Faculty of Health and Wellbeing, Sheffield Hallam University, Sheffield, UK
2. Institute of Occupational and Social Medicine, Medical Faculty, RWTH Aachen University, Aachen, Germany
3. University of Warwick, Warwick Medical School, Health Sciences Research Institute, Warwick, UK
4. Department of Statistics, Stockholm University, Stockholm, Sweden
**Correspondence to k.khatab@shu.ac.uk*

Disclosure: No potential conflict of interest.

ABSTRACT

The aim of this study was to examine the association between workplace exposure to asbestos and risk factors for developing related chronic respiratory diseases, using the analysis of a cohort of 8,582 formerly asbestos-exposed workers, as well as to assess the grade value of three risk categories used for a focused surveillance procedure. The results showed that the participants who were aged over 65 (OR and 95% CI: 11.47 [5.48-23.99]) and active smokers (OR and 95% CI: 9.48 [4.07-22.09]), were at a significantly high risk for developing lung cancer. The risk of developing benign lesions of the lung or pleura (BLLP) was almost 6-times higher (OR and 95% CI: 5.76 [4.7-7]) for the age group over 65. The risk of developing mesothelioma was influenced by exposure duration (OR and 95% CI: 4.36 [1-19.01]); and for the age group over 65 (OR and 95% CI: 4.58 [1.86-11.27]). The study has demonstrated that the use of risk categories based on a combination of risk factors (age, smoking status, and duration of exposure) could be advantageous for planning the target health surveillance programmes.

Keywords: Epidemiology, lung cancer, mesothelioma, asbestos.

INTRODUCTION

Epidemiological evidence suggests a strong association between workplace exposure to airborne asbestos fibres and diseases such as lung cancer (LC), mesothelioma, asbestosis, and benign pleural lesions. The development of asbestos-related diseases is influenced by the combined effects of the individual's cumulative exposure, age, smoking habits, and other factors such as type of asbestos, age at the beginning of exposure, and time since first exposure. Occupational exposure to asbestos has been identified as a risk factor for developing diseases such as LC, mesothelioma, and benign lesions of the lung or pleura (BLLP). After being widely used during the 1960s and 1970s, asbestos was banned from workplace environments in many countries, but it is still exported to some developing countries.

Due to the long median latency period (35-40 years) for developing asbestos related chronic diseases, it is difficult to assess the impact of exposure.[1] Few previous studies on asbestos exposure assessments have been reported.[2-4] The Asbestos Surveillance Programme Aachen (ASPA) was the first time where an effort was made to assess in detail the asbestos exposure in power industry workers. Because of the exposure characteristics in this cohort, a large number of asbestos related diseases were expected.[5-7] Therefore, there was a need for a surveillance programme to improve early detection. Thus, in the ASPA, a cohort of formerly exposed power plant workers was chosen for a prospective study, using radiological imaging techniques for the early detection of asbestos-related diseases.

The previous ASPA study focused on proposing a basic strategy for this health surveillance and assessing asbestos exposures in various occupational groups in the power industry.[5-7] This study focused on the prevalence of asbestos-related diseases in the select cohort subgroups, which have been followed in the framework of ASPA. The work started with a descriptive analysis of three asbestos exposed sub-cohorts of workers from different types of jobs in the power industry, then assessed the difference between the three sub-cohorts with regards to their corresponding levels of risk. Furthermore, we investigated how well the risk categories, using a multiplicative model including age, years of exposure, and smoking habits, could predict the risk of asbestos-related disease in comparison to applying a sole risk factor. The information about the exposure to asbestos fibres and the three different types of power industry was published in Felten et al.[5]

MATERIALS AND METHODS

Study Participants

Starting in the 1990s, a major power plant company sent a short questionnaire to all active and former workers, who, according to the employers' records, had been exposed to asbestos dusts. At baseline, approximately 20,000 workers were approached using an assessment-survey and requested to participate in an evaluation and follow-up study. Around 11,000 workers replied to this survey and 8,582 gave their consent to take part in the ASPA. They were recruited from March 2002-December 2006.

ASPA

From 2002-2009, the Institute of Occupational Health, RWTH Aachen University, Germany, together with various partners, carried out a surveillance programme aimed at the early detection and treatment of asbestos-related diseases and evaluated the risk factors which caused the asbestos-related diseases in this cohort. The aim of the surveillance programme was to check, whether a risk-based examination strategy would be useful for creating an efficient tool for the prospective surveillance of former asbestos workers. LC was the primary target for the selection of risk groups, because i) it is a relevant and frequent malignant disease with known risk factors, ii) it has long been known that early detection could lead to a stage shift towards treatable cases, and iii) a benefit of early detection impacting mortality reduction was expected, and which has now been demonstrated.[6,7] The cohort consisted of 8,582 formerly asbestos-exposed workers who came from three different types of power industry: power generation workers (n=5,620), power distribution workers (n=2,469), and gas supply workers (n=480). A detailed description of the exposure of the cohort has been published in 2010.[5] Of the 8,582 participants, 7,062 (82%) were examined for evidence of lung-related diseases in the time period between 2002 and 2009.

Risk Model

As the cohort groups were heavily exposed to asbestos in the different work places, an empiric risk classification was used to classify and distinguish between the highest risk group and the lowest risk group. This model was constructed on the knowledge that the age of participants, and smoking habits, combined with long asbestos exposure, led to a multiplicative increase in the LC risk.[2] Based on a multiplicative relationship of these factors, the cohort has been divided into three subgroups. Group A is a group with the comparatively highest risk, group B is intermediate-risk group, and group C is a comparatively low-risk group. In group A the medical examination included a standardised questionnaire, a physical examination with lung function testing, and low-dose spiral computed tomography (LDSCT) at 12 month intervals. In group B, the examination included a standardised questionnaire, a physical examination, a standard chest X-ray at 12 month intervals. In group C the examination included a standardised questionnaire, a physical examination, and a standard chest X-ray at 36 month intervals. This risk model was adapted and applied in Das et al.[3]

Statistical Analyses

We first used simple descriptive analysis to investigate the characteristics of the different risk factors according to three risk groups and the industrial groups. Then the logistic model was applied to assess the association between the risk factors and the health outcomes. The most influential variables (e.g. age, duration of exposure, latency time, age at first exposure, and history of smoking) on the asbestos lung related diseases were included in this model after reviewing the relevant studies.[8-10] To assess these associations between the risk factors and the outcome variables (LC, BLLP, and mesothelioma), the logistic model was applied, as has been in some previous studies.[11] Descriptive statistics were presented in order to summarise the characteristics of the three industrial groups, as well as the three risk groups (Table 1,2).

Bivariate logistic analysis was done to assess the hypotheses of association between the risk factors, along with the risk groups, and the diseases (Table 3). A separate logistic analysis was performed to examine the association between risk factors and outcome variables (Table 3). All computations were carried out with Stata® 11 Software.

RESULTS

The study also showed that out of the 8,582 participants, who were exposed to asbestos, there were 49 cases of mesothelioma, 107 cases with LC, and 768 had BLLP. The distribution of risk factors and diseases among three risk groups showed that 25.9% had BLLP in risk group A, 19.6% in risk group B, and 5.1% in risk group C. From group A, 5.2% had LC, followed by 3.0% in group B, and 0.5% in group C; while only 0.4% and 0.3% in the risk groups A and C, respectively, had mesothelioma. A much higher percentage cold be found in risk group B, with 1.6%, who were affected by mesothelioma. Group A was the oldest with the longest time of exposure duration and latency, followed by group B and C.

The main characteristics of the three groups indicated that the power generation workers, who represented approximately two-thirds (65%) of all participants, were 10 years older (61.9 versus 51.5 years) than the second largest group of the 2,469 (29%) power distribution workers, and had a much longer mean period of asbestos exposure (18.9 versus 12.5 years). The 480 gas supply workers (6% of the total) had a similar mean age of 59.8 years, but their mean period of asbestos exposure of 15 years was closer to those of the power distribution group. Furthermore, the gas supply workers had the longest latency period, as they had started working at an earlier age (23.9 years).

Of the power generation workers (n=5,620), there were 8% allocated in high-risk group A, 23.4% in risk group B, and the remaining cases (68.6%) in low-risk group C. Tables 1 and 2 provide information on the distribution of risk factors and diseases among the industrial groups as well as among the risk groups. The majority of the participants (28.8%) in this group were 65-75 years of age followed by 55-65 (23.7%) years of age, and 13.8% were over 75 years of age (Table 1). About 39.3% of this group were ex-smokers and 25.2% were active smokers, while 39.7% had been exposed to over 20 years to asbestos, followed by 35.3% who had been exposed to asbestos for between 10-20 years. The results showed that the power generators were more affected by BLLP as 17.8% (Table 2) of BLLP cases were classified in risk group A, while 41% were allocated either in the risk groups B or C. The results also show, that out of 97 (1.7%) cases who were affected by LC, 43% were in risk group B, while 24% were found in high-risk group A. In the power generation group there were 48 (0.8%) cases of mesothelioma. Half of these cases were allocated to risk group B while 43% were allocated to low-risk group C.

The majority of the power distribution workers (n=2,469) were included in low-risk group C (89.6%), while only 1.9% were allocated in high-risk group A, and the remaining in risk group B (8.5%). As the majority of this group were in a lower risk group, none had mesothelioma, only 0.36% had LC, and 2.87% had BLLP. Compared to the power generation group, the power distribution group was younger (only 16.7% were over 65 years). 18.2% of this group were active smokers and 37.5% were ex-smokers. Only 3.9% of this group had been exposed, over 30 years, to asbestos, and 16% were exposed over 20 years (Tables 1 and 2). Regarding the gas supply workers, there were only 480 participants included in this group, of which about 94.8% were allocated in risk group C, 4.6% were in risk group B, and the remaining in risk group A (0.6%). About 3.75% of the participants had BLLP; 0.2% had LC, and 0.2% also had mesothelioma. About 49% of the participants in this group were ex-smokers while 15% were active smokers. About 32% were over 65 years of age (Tables 1 and 2).

The risk of having BLLP, LC, and mesothelioma were higher (Table 3) among those who were over 65 years of age, had a long period of exposure and latency (over 10 years and 20 years, respectively), and were smokers. The results showed that the risk of having diseases was very high among those who were classified in high-risk group A, followed by group B, and lowest for those in low-risk group C. For instance, the risk of having LC for those who were allocated to high-risk group A was 10-times higher (OR and 95% CI: 10.5 [6.2-17.6]) compared to those who were in low-risk group C. Findings from multiple logistic analysis (Table 3) confirmed a positive association commonly found between the three diseases (BLLP, LC, and mesothelioma) and most of the risk factors (aged over 65, exposure duration over 10 years, latency period over 20 years, active smokers, age at first exposure, and most of the considered occupational groups). However, latency has only a small association with BLLP.

DISCUSSION

The comparatively high detection rates of BLLP and LC in high-risk group A (Table 3) may have been partly due to the radiological examination method using LDSCT rather than standard chest X-ray. The study design required the use of CT scan in the high-risk group (A), which is more sensitive for the detection of typical changes associated with BLLP and small lung nodules.

BLLP

The adjusted risk of getting BLLP was almost 6-times higher (OR and 95% CI: 5.76 [4.7-7]) for the older age group (over 65) compared to the younger age group (under 65) (Table 3). We interpreted the finding that adjusted and unadjusted odds ratio (ORs) for age were similar (Table 3), as an indication of a strong age dependency of BLLP changes, whereas the ORs for exposure duration and latency were much smaller in the adjusted analysis. Exposure duration and latency were far less important and showed a significant influence only when exceeding periods of 10 and 20 years. These results were consistent with many previous studies which confirmed that the latency period for BLLP was usually at least 10 years and that the higher the exposure, the greater the chances of developing the disease.[12-22] Smoking habits also played a significant role in developing BLLP as the results showed that the risk of having BLLP for those who were active smokers and for the ex-smokers were 2-times (OR and 95% CI: 1.9 [1.5-2.4]) and 1.5-times higher (OR and 95% CI: 1.55 [1.26-1.89]), respectively, compared to those who were non-smokers, which is consistent with the findings by Hammond et al.[2] When considering occupational tasks, the results showed that all occupations in the power generationand distribution groups were at higher risk of having BLLP compared to the gas supply group. The metalworkers were those with the highest ORs (OR and 95% CI: 4.79 [2.8-7.96]), followed by the plant operators group (OR and 95% CI: 3.32 [1.99-5.55]).

Lung Cancer

Some studies showed that those who have smoked for 20 years have a risk of LC about 15-times greater than that of lifelong non-smokers. In addition, if the smokers have had asbestos exposure sufficient to cause asbestosis, this risk is multiplied 5-fold, so they are about 55-times more likely to get LC than a non-smoking, non-asbestos exposed individual, according to Selikoff et al.[8] The results of our study confirmed the associations between LC and smoking, exposure duration, occupational tasks (e.g. metalworkers, plant operator, other occupation, etc.), and age. The association between LC and the older age group (65) was 11-times greater (OR and 95% CI: 11.47 [5.48-23.99]) compared to the younger group (under 65 age) (Table 3). Furthermore, the risk of getting LC was 9-times higher (OR and 95% CI: 9.48 [4.07-22.09]) for active smokers compared to those who were non-smokers. More than 84% of those who had LC were either ex or current smokers. In our cohort, smoking had a strong association with LC, as was also reported in many previous studies. However, in ex-smokers the risk of LC was only half the risk found for active smokers (Table 3). The effect of years of asbestos exposure (OR and 95% CI: 2.79 [0.69-11.28]) and time since first exposure (OR and 95% CI: 0.79 [0.16-3.9]) on the risk of LC was small, compared to age and smoking habits.

Mesothelioma

Some studies showed that the incidence of mesothelioma is proportional to the fibre concentration to which the workers were exposed, and to time since first exposure for both workers and the general population. However, the risk of mesothelioma is probably more influenced by the type of asbestos and the time since first exposure than the fibre concentrations, and the duration of exposure or the cumulative exposure.[23] However, in our study the exposure duration showed a significant effect with an OR of 4.36 (CI: 1-19.01), while the time since first exposure showed no effect. It is well documented that the incidence of mesothelioma is highest in those who have worked directly with asbestos.[18] However, the amount of exposure necessary to cause mesothelioma is considerably less than that associated with asbestosis and LC, and there may even be a risk for people who have had regular contact through the washing of workers dust-laden clothes, or those who had lived close to asbestos factories in the past.

According to Peto,[23] the most worrying aspect is the discovery that the rate of mesothelioma deaths is rising in men aged 50 and younger, and that most victims have only had secondary links with asbestos, often as construction workers, carpenters, plumbers, or electricians.[23] In our study, the metalworker group was the most affected group by mesothelioma (OR and 95% CI: 4.62 [0.6-35.03]), as these workers had the highest exposure duration combined with cumulative exposure (Table 3).[5] Also our results suggested that the risk of having mesothelioma was confounded by exposure duration (OR and 95% CI: 4.36 [1-19.01]). Smoking habits had no association with mesothelioma, which was consistent with published reports.[24-28]

CONCLUSIONS

The results confirmed that the older participants who were active smokers with long-term exposure to asbestos were at the greatest risk of getting BLLP and LC. The risk increased for people who had 10 years or more exposure.The risk of getting BLLP and LC was strongly increased for those who were active smokers. The use of risk categories based on a combination of risk factors (age, smoking status, and duration of exposure) would be advantageous for planning targeted health surveillance programmes. This evaluation contributes to the effort of identifying characteristics which lead to an increased risk of developing asbestos-related diseases in power industry workers, which is a precondition for a risk differentiated approach of early disease detection in that group.

Table 1: Distribution of workers by age, exposure duration, and smoking status by risk categories accross industry groups.

	Power generation workers				Power distribution workers				Gas supply workers			
Covariates	A	B	C	Total	A	B	C	Total	A	B	C	Total
Age												
Under 45	0	0	586 (100.0)	586 (10.4)	0	0	816 (100.0)	816 (33.0)	0	0	47 (100.0)	47 (9.8)
45-54	0	101 (7.7)	1208 (92.3)	1309 (23.3)	0	39 (11.0)	846 (95.6)	885 (35.8)	1 (0.9)	2 (1.9)	103 (97.2)	106 (22.1)
55-64	40 (3.0)	282 (21.2)	1011 (75.8)	1333 (23.7)	5 (1.4)	39 (11.0)	311 (87.6)	355 (14.4)	0	5 (2.9)	168 (97.1)	173 (36)
65-74	221 (13.7)	578 (35.7)	818 (50.6)	1617 (28.8)	19 (6.1)	97 (31.1)	196 (62.8)	312 (12.6)	2 (1.6)	13 (10.6)	108 (87.8)	123 (25.6)
Over 74	188 (24.3)	353 (45.7)	232 (30.0)	773 (13.8)	23 (22.8)	36 (35.6)	42 (41.6)	101 (4.1)	0	2 (6.5)	29 (93.5)	31 (6.5)
	449 (8.0)	**1314 (23.0)**	**3855 (69.0)**	**5618**	**47 (1.9)**	**211 (8.5)**	**2211 (89.5)**	**2469**	**3 (0.6)**	**22 (4.6)**	**455 (93.7)**	**480**
Exposure Duration (years)												
<1	0	0	60 (100.0)	60 (1.1)	0	0	0	0	0	0	2 (100.0)	2 (0.4)
1-10	0	13 (1.0)	1329 (99.0)	1342 (23.9)	0	4 (0.4)	993 (99.6)	997 (46.6)	0	1 (0.4)	173 (99.6)	174 (37.3)
10-20	68 (3.4)	373 (18.8)	1540 (77.7)	1981 (35.3)	8 (1.0)	82 (10.4)	701 (88.6)	791 (37.0)	2 (1.2)	8 (4.7)	160 (94.1)	170 (36.4)
20-30	176 (13)	550 (40.7)	625 (46.3)	1351 (24.0)	13 (4.9)	94 (35.5)	158 (59.6)	265 (12.4)	0	8 (9.6)	75 (90.4)	83 (17.3)
30-40	162 (20.6)	339 (43.0)	287 (36.4)	788 (14.0)	21 (26.9)	30 (38.5)	27 (34.6)	78 (3.6)	1 (3.2)	4 (12.9)	26 (83.9)	31 (6.6)
Over 40	43 (44.8)	39 (40.6)	14 (14.6)	96 (1.7)	5 (71.4)	1 (14.3)	1 (14.3)	7 (0.3)	0	1 (14.3)	6 (85.7)	7 (1.5)
	449 (8.0)	**1314 (23.0)**	**3855 (69.0)**	**5618**	**47 (1.9)**	**211 (8.5)**	**1880 (88.0)**	**2138**	**3 (0.6)**	**22 (4.7)**	**442 (94.7)**	**467**
Smoking												
Non smoker	0	33 (1.7)	1965 (98.3)	1998 (35.6)	0	1 (0.1)	1074 (99.9)	1075 (44.3)	0	0	170 (100.0)	170 (35.9)
Ex-Smoker	93 (4.2)	893 (40.4)	1223 (55.4)	2209 (39.3)	20 (2.2)	129 (14.2)	761 (83.6)	910 (37.5)	1 (0.4)	13 (5.3)	218 (94.4)	231 (49.0)
Smoker	356 (25.2)	388 (27.5)	669 (47.3)	1413 (25.1)	27 (6.1)	81 (18.4)	333 (75.5)	441 (18.2)	2 (2.8)	9 (12.7)	60 (84.5)	71 (15.0)
	449 (8.0)	**1314 (23.0)**	**3857 (69.0)**	**5620**	**47 (1.9)**	**211 (8.5)**	**2168 (89.6)**	**2426**	**3 (0.6)**	**22 (4.6)**	**448 (94.7)**	**473**

Figures in parentheses are percentage distribution amongst A, B, and C risk categories; under 'Total' these are column distribution.

Table 2: Distribution of workers by disease, age at exposure, latency, and occupation by risk categories accross industry groups.

	Power generation workers (n=5,620)				Power distribution workers (n=2,469)				Gas supply workers (n=480)			
Disease	A	B	C	Total	A	B	C	Total	A	B	C	Total
BLLP												
No	328 (6.6)	1035 (20.9)	3578 (72.4)	4941 (87.9)	39 (1.6)	188 (7.8)	2171 (90.5)	2398 (97.1)	3 (0.6)	21 (4.5)	438 (94.8)	462 (96.2)
Yes	121 (17.8)	279 (41.1)	279 (41.1)	679 (12.1)	8 (11.3)	23 (32.4)	40 (56.3)	71 (2.9)	0	1 (5.6)	17 (94.4)	18 (3.8)
Lung Cancer												
No	425 (7.7)	1272 (23)	3826 (69.3)	5523 (98.3)	45 (1.8)	206 (8.4)	2209 (89.6)	2460	3 (0.6)	22 (4.6)	454 (94.8)	479 (99.8)
Yes	24 (24.7)	42 (43.3)	31 (32)	97 (1.7)	2 (22.2)	5 (55.6)	2 (22.2)	9 (0.36)	0	0	1 (100)	1 (0.2)
Mesothelioma												
No	447 (8)	1289 (23.1)	3836 (68.8)	5572 (99.1)	47 (1.9)	211 (8.5)	2211 (89.6)	2469	3 (0.6)	22 (4.6)	454 (94.8)	479 (99.8)
Yes	2 (4.2)	25 (52.1)	21 (43.8)	48 (0.9)	0	0	0	0	0	0	1	1 (0.2)
Age at first exposure												
≤25	219 (6.7)	693 (21.3)	2342 (72)	3254 (58)	33 (1.9)	139 (8)	1557 (90.1)	1729 (70)	3 (1.1)	15 (5.4)	259 (93.5)	277 (57.7)
>25	230 (9.8)	619 (26.3)	1507 (64)	2356 (42)	14 (3.1)	72 (15.8)	370 (81.1)	456 (18.5)	0	7 (3.8)	179 (96.2)	186 (38.8)
Latency												
≤20 years	0	10 (1.1)	939 (98.9)	949 (16.8)	0	0	416 (100)	416 (16.8)	0	0	42 (100)	42 (8.8)
>20 years	265 (7.6)	992 (28.4)	2240 (64.1)	3497 (62.3)	47 (2.7)	211 (11.9)	2240 (64.1)	1769 (71.7)	3 (0.7)	22 (5.2)	396 (94.1)	421 (87.7)
Occupation												
Metalworker	129 (8.1)	367 (22.9)	1104 (69)	1600 (28.4)	0	6 (12.2)	43 (87.8)	49 (2)				
Electrician	36 (5.5)	137 (21)	479 (73.5)	652 (11.6)	32 (1.7)	163 (8.8)	1665 (89.5)	1860 (75.3)				
Plant operator	123 (7.7)	390 (24.6)	1075 (67.7)	1588 (28.2)	0	3 (23.1)	10 (76.9)	13 (0.5)				
Other craftsmen	25 (4.2)	99 (16.5)	477 (79.4)	601 (10.7)	8 (3.3)	21 (8.6)	215 (88.1)	244 (10)				
Supervisor	19 (9)	38 (18.1)	153 (72.9)	210 (3.7)	3 (1.9)	9 (5.7)	146 (92.4)	158 (6.4)				
Other occupation	48 (7.6)	169 (26.7)	415 (65.7)	632 (11.2)	4 (2.9)	9 (6.4)	127 (90.7)	140 (5.6)				
Gas									3 (0.6)	22 (4.6)	455 (94.8)	480

Figures in parentheses are percentage distribution amongst A, B, and C risk categories; under 'Total' these are column distribution; BLLP: benign lesions of the lung or pleura.

Table 3: Association between risk factors and diseases (bivariate analysis), adjusted odds ratios across risk factors, and three diseases.

		BLLP		Lung Cancer		Mesothelioma	
Factors	Levels	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Age	≤65 (ref)	1	1	1	1	1	1
	>65*	6.3 (5.3-7.44)	5.75 (4.7-7)	11.99 (6.93-20.74)	11.47 (5.48-23.99)	8.54 (4.14-17.63)	4.58 (1.86-11.27)
Exposure Duration	≤10 years (ref)	1	1	1	1	1	1
	>10 years*	7.67 (5.71-10.32)	2.14 (1.5-3.06)	7.8 (3.42-17.8)	2.79 (0.69-11.28)	10.8 (2.62-44.53)	4.36 (1-19.01)
Latency	≤20 years (ref)	1	1	1	1	1	1
	>20 years	13.64 (8.01-23.24)	3.29 (1.79-6.06)	6.26 (1.3-7.3)	0.79 (0.16-3.9)	7.7 (1.05-56.59)	0.21 (0.25-1.19)
Smoking	Non smoker (ref)	1	1	1	1	1	1
	Ex-Smoker	1.94 (1.6-2.3)	1.55 (1.26-1.89)	3.1 (1.82-5.28)	4.1 (1.84-9.25)	1.51 (0.83-2.73)	0.49 (0.69-3.32)
	Smoker	1.4 (1.13-1.7)	1.9 (1.5-2.4)	3.03 (1.69-5.42)	9.48 (4.07-22.09)	0.28 (0.08-0.95)	0.19 (0.02-1.52)
Age at first exposure	≤25	1.18 (1.02-1.38)	0.81 (0.67-0.97)	2.8 (1.93-4.24)	0.62 (0.28-1.36)	1.21 (0.68-2.14)	0.62 (0.28-1.36)
	>25 (ref)	1	1	1	1	1	1
Occupation	Metalworker*	4.8 (2.94-7.8)	4.79 (2.8-7.96)	6.85 (0.95-51.26)	9.7 (1.3-71.7)	6.47 (0.87-48.17)	4.62 (0.6-35.03)
	Electrician*	1.3 (0.79-2.18)	1.73 (1.02-2.0)	3.3 (0.42-25.58)	3.44 (0.45-25.8)	1.14 (0.13-9.5)	0.98 (0.109-8.8)
	Plant operator*	3.7 (2.31-6.2)	3.32 (1.99-5.55)	4.39 (0.58-33.19)	8.2(1.11-6.06)	2.4(0.3-19.28)	1.34 (0.15-11.64)
	Other crafts-men	1.8 (1.05-3.1)	2.2 (1.25-3.08)	2.27 (0.25-20.69)	2.27 (0.25-20.39)	0.56 (0.03-9.07)	0.66 (0.04-10.69)
	Supervisor	2.1 (1.19-4)	2.7 (1.44-5.15)	1.18(0.07-19.29)	1.30(0.08-20.87)	1.3(0.081-20.87)	1.67 (0.1-27.08)
	Other occupation	2.28 (1.3-3.9)	2.58(1.47-4.54)	5.47 (0.68-44.04)	9.49 (1.24-72)	4.38 (0.53-35.7)	1.33 (0.11-14.97)
	Gas (ref)	1	1	1	1	1	1
Risk Groups	A*	6.43(5.1-8.08)	1	10.5 (6.2-17.6)	9.5 (5.6-14.6)	1.9 (0.5-5.08)	1.2 (0.27-4.7)
	B*	4.49 (3.8-5.3)	6.2 (4.8-7.8)	5.99 (3.8-9.3)	4.8 (3.2-7.6)	4.8 (2.7-8.64)	4.1 (2.1-7.8)
	C (ref)	1	4.1 (3.6-4.9)	1	1	1	1

* Statistically significant at p<0.05.

Unadjusted and adjusted for age, exposure duration, latency, smoking, age at first exposure, and occupation; BLLP: benign lesions of the lung or pleura.

Acknowledgements

Authors would like to thank The Central Registration Agency for Employees Exposed to Asbestos Dust (GVS), which supported the study by organising the registration of the participants. We would like to express our thanks to The German Social Accident Insurance Institution for the energy, textile, electrical, and media products sectors (BGETEM), Cologne, Germany, which supported the study financially and in other ways. Particular thanks go to Dr Johannes Hüdepohl and Dr Wolfgang Zschiesche of BGETEM for their special support. The authors wish to thank Dr Christian Feldhaus and Dr Hans Joachim Majunke of RWE Power AG, Essen, Germany, for their support in building the cohort and organising their investigation. This study was supported by unrestricted grants to the University Hospital Aachen, from the German Social Accident Insurance Institution for the energy, textile, electrical, and media product sectors (BGETEM, grant number 360057) and the company RWE Power AG (grant number 370221). We are also grateful to Kathy Bischof for reviewing the manuscript.

REFERENCES

1. Kishimoto T et al. Clinical study of asbestos-related lung cancer. Ind Health. 2003;41(2):94-100.

2. Hammond EC et al. Asbestos exposure, cigarette smoking and death rates. Ann N Y Acad Sci. 1979;330:473-90.

3. Das M et al. Asbestos Surveillance Program Aachen (ASPA): initial results from baseline screening for lung cancer in asbestos-exposed high-risk individuals using low-dose multidetector-row CT. Eur Radiol. 2007;17(5):1193-9.

4. Kraus T et al. Recommendations for reporting benign asbestos-related findings in chest X-ray and CT to the accident insurances. Pneumologie. 2009;63:726-32.

5. Felten MK et al. Retrospective exposure assessment to airborne asbestos among power industry workers. J Occup Med Toxicol. 2010;5:15.

6. Aberle DR et al. The National Lung Screening Trial: overview and study design. Radiology. 2011;258(1):243-53.

7. Henschke CI et al. Early Lung Cancer Action Project: overall design and findings from baseline screening. Lancet. 1999;354(9173):99-105.

8. Selikoff IJ et al. Mortality experience of insulation workers in the United States and Canada, 1943--1976. Ann N Y Acad Sci. 1979;330:91-116.

9. Cureton RJ. Squamous cell carcinoma occurring in asbestosis of the lung. Br J Cancer. 1948;2(3):249-53.

10. Doll R. Mortality from lung cancer in asbestos workers. Br J Ind Med. 1955;12(2):81-6.

11. Beate P. Cancer mortality in a surveillance cohort of German males formerly exposed to asbestos. Int J Hyg Environ Health. 2010;213(1):44-51.

12. Hagemeyer O et al. Asbestos consumption, asbestos exposure and asbestos-related occupational diseases in Germany. Int Arch Occup Environ Health. 2006;79(8):613-20.

13. Park EK et al. Asbestos-related occupational lung diseases in NSW, Australia and potential exposure of the general population. Ind Health. 2008;46(6):535-40.

14. Valeyre D, Letourneux M. [Asbestosis]. Rev Mal Respir. 1999;16(6 Pt 2):1294-307.

15. Manning CB et al. Diseases caused by asbestos: mechanisms of injury and disease development. Int Immunopharmacol. 2002;2(2):191-200.

16. Weill H et al. Changing trends in US mesothelioma incidence. Occup Environ Med. 2004;61(5):438-41.

17. Bernstein DM, Hoskins JA. The health effects of chrysotile: current perspective based upon recent data. Regul Toxicol Pharmacol. 2006;45(3):252-64.

18. National Occupational Health and Safety Commission. Worksafe Australia. Guidance note on the interpretation of exposure standards for atmospheric contaminants in the occupational environment [NOHSC:3008(1995)] 3rd edition (Updated November 2001). National standards, codes of practice and related guidance.

19. Health and Safety Executive in the United Kingdom. The control of asbestos regulations 2006. A guide for safety representatives. 2006.

20. Hillerdal G, Henderson DW. Asbestos, asbestosis, pleural plaques and lung cancer. Scand J Work Environ Health. 1997;23(2):93-103.

21. Peacock C et al. Asbestos-related benign pleural disease. Clin Radiol. 2000;55(6):422-32.

22. Hessel PA et al. Asbestos, asbestosis, and lung cancer: a critical assessment of the epidemiological evidence. Thorax. 2005;60(5):433-6.

23. Peto J, “Dose and time relationships for lung cancer and mesothelioma in relation to smoking and asbestos exposure,” Fischer M, Meyer E (eds.), Zur Beurteilung der Krebsgefahr durch Asbest [Assessment of the cancer risk of asbestos] (1984), Munich: Medizin Verlag, pp. 126-32.

24. Robinson BW, Lake RA. Advances in malignant mesothelioma. N Engl J Med. 2005;353:1591–603.

25. Berry G et al. Combined effect of asbestos and smoking on mortality from lung cancer and mesothelioma in factory workers. Br J Ind Med. 1985;42(1):12-8.

26. Weatherall DJ et al (eds.), Oxford Textbook of Medicine (1996) 3rd edition, Oxford: Oxford University Press.

27. Neumann Vet al. Malignant mesothelioma--German mesothelioma register 1987-1999. Int Arch Occup Environ Health. 2001;74(6):383-95.

28. Burdorf A et al. Occupational characteristics of cases with asbestos-related diseases in the Netherlands. Ann Occ Hygiene. 2003;47(6):485-92.