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Relation between asbestosis and bronchial cancer in amphibole asbestos miners

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ABSTRACT In a necropsy series of 339 amphibole asbestos miners heavy smoking, age, and the presence of asbestosis were significantly associated with the presence of bronchial cancer. Of the 35 cases of bronchial cancer, 24 were associated with asbestosis. Eleven cases of bronchial cancer occurred in men without asbestosis; all were smokers. Standardised proportional mortality rates indicated no excess of bronchial cancer in 302 exposed men without asbestosis whereas these rates were progressively raised in men with slight or moderate/severe asbestosis. Of the four exposure variables introduced separately into a logistic regression model, "years of exposure" made a small but significant contribution; "residence time" marginally failed to achieve a 5% level of significance. Two other exposure variables tested including cumulative fibre exposure (fibre years) made no significant contribution. In the absence of asbestosis at necropsy a bronchial cancer in a man exposed to asbestos is unlikely to be due to asbestos.

The question of whether the presence of parenchymal asbestosis is a necessary prerequisite to attribute a bronchial cancer to inhalation of asbestos is controversial. Some compensation authorities insist that asbestosis must be shown before compensation is granted. Furthermore, some authorities believe that the dose of respirable asbestosis dust that will cause bronchial cancer is about the same[1] or even greater[2] than that which will cause asbestosis.

The object of the present study was to determine if any parameters of exposure to asbestos dust exert any additional risk of developing bronchial cancer after allowing for the presence of asbestosis.

Materials and methods

A mortality study on all white men identified from company records who were employed by amphibole asbestos mines (crocidolite and amosite) in South Africa is being analysed. Records regarding employees were preserved by different companies from between 1945 and 1956. At the latter date the keeping of records became compulsory. Black employees were not considered in this study because of inadequacies of registration of causes of death and poor smoking and exposure data. Altogether 7318 men were identified and death certificates sought at the Department of the Interior. Of these, 1165 (15·9%) had died by 31 December 1980 and their death certificates were obtained. Necropsies had been performed on 427 (36·7%) of the men and the reports of pathologists (staff of the National Centre for Occupational Health) on macroscopic and histological findings in the lungs were available. These reports indicate whether asbestosis was present, its grade, and whether bronchial cancer was present (table 1).

Asbestosis was graded as follows: slight asbestosis implies organisation of alveolar spaces with some interstitial thickening due to collagen or reticulin with areas of normal lung. In moderate asbestosis changes are more extensive but less so than in pronounced asbestosis. Pronounced asbestosis implies organisation of alveolar spaces and fibrosis of alveolar walls to the extent that there is no normal lung or massive fibrosis even without the above. In all cases asbestosis bodies or fibres must be present.

An unmatched case referant design was adopted for the study. The cases were 35 individuals with bronchial cancer as identified by necropsy. Ten of the 35 cases had no mention of bronchial carcinoma on the death certificate, yet, in eight of these necropsy clearly proved that bronchial cancer was the cause of death. In two cases the cause of death was not so certain. In one there was a bronchial adenocarcinoma with metastases but evidence of extensive non-asbestotic fibrosis of the lungs leading to severe cor pulmonale. In the second case obstructive airways disease appeared to be the cause of death but a small oat cell

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Table 1 *Cases of bronchial cancer and referents by smoking status and degree of asbestosis*

	Cases	Referents
Smoking status:	*No (%)*	*No (%)*
Never	2 (5·7)	35 (9·6)
Ex	6 (17·1)	36 (9·9)
Light	5 (14·3)	70 (19·2)
Moderate	11 (31·4)	175 (48·1)
Heavy	11 (31·4)	48 (13·2)
Total	35	364
Asbestosis:		
None	11 (31·4)	291 (79·9)
Slight	15 (42·9)	54 (14·8)
Moderate/pronounced	9 (25·7)	19 (5·2)
Total	35	364

bronchogenic carcinoma was also found at necropsy. The latter two were included among the cases.

Data of smoking habits were not available in 28 men (none with bronchial cancer) and they were excluded from the analysis. The group for the study therefore comprised 399 men (table 1). The referents were the 364 men without bronchial cancer who had smoking data.

The files of the cases and referants kept by the Medical Bureau for Occupational Disease (MBOD) were searched for details of exposure to asbestos and other mining dust and for smoking habits. Smoking habit was taken as the number of cigarettes or equivalents for cigars or pipe recorded in the last MBOD clinical examination before death. Smoking status was categorised as never a smoker, ex-smoker (cessation more than two years before date of examination), current light smoker (1–9 cigarettes a day), current moderate smoker (10–19 cigarettes a day), and current heavy smoker (20 or more cigarettes a day) (table 1).

Years of exposure to asbestos and residence time (time of first exposure to date of death) were known from the MBOD files. Dose of asbestos was computed by multiplying the measured fibre/ml levels for each mine, occupation and calendar period by time a man had worked in each occupation, and summing the various exposures over his career and expressing the result as fibre years.

The residence time weighted dosage (residence TWD) as described by Finkelstein[3] was also computed (table 2).

To model the effect of exposure to asbestos on the risk of developing bronchial cancer when adjusting for the effects of smoking habits, age, and asbestosis, an unconditional logistic regression analysis was performed using the program "RISK."[4]

As exposure to asbestos was expressed in four ways (years of exposure, residence time, fibre years, and residence TWD), four models were created to analyse each exposure variable uniquely with smoking, age, and asbestosis. For the categorical variables smoking and asbestosis, design (indicator) variables were generated to contrast each category with the baseline category (no smoking and no asbestosis respectively) by the "partial" coding scheme.[5]

To test how adequately the models fitted the data, smoking, age, asbestosis, and the respective exposure to asbestos variables were entered in a stepwise manner in that order, and the goodness of fit χ^2 was tested for significance using the change in the log likelihood χ^2 ratio.[6] Odds ratios were determined from the regression coefficients as estimators of increased risk of bronchial cancer.

To test how the prevalence of bronchial cancer in the three groups, no asbestosis, slight asbestosis, and moderate pronounced asbestosis, compared with the age, race, and sex standardised rate in the white male population of South Africa, three standardised proportional mortality rates (SPMR) were estimated.

Results

The fit of the model to the data improved as each of the variables smoking, age, and asbestosis was entered (table 3). The most significant contributor in predict-

Table 2 *Means and standard deviations (SD) for age and exposure to asbestos by cases of bronchial cancer and referents*

	Cases (n = 35)		Referents (n = 364)	
	Mean	*(SD)*	*Mean*	*(SD)*
Age	59·5	(8·4)	51·4	(12·1)
Years exposure	11·2	(8·2)	4·2	(6·0)
Residence time	21·3	(7·0)	14·6	(8·2)
Fibre years	73·7	(153·7)	23·7	(88·3)
Residence TWD	1202·2	(2808·0)	385·7	(2163·6)

TWD = Time weighted dosage.

Table 3 *Goodness of fit χ^2 values for the stepwise logistic regression analyses*

Model	Step	Term entered	Improvement in LR χ^2†	Degree of freedom	p Value
	1	Smoking	10·13	4	0·04
	2	Age	14·83	1	0·0001
	3	Asbestosis	30·1	2	<0·0001
1	4	Years exposure	6·36	1	0·01
2	4	Residence time	2·78	1	0·10
3	4	Fibre years	0·11	1	0·74
4	4	Residence TWD	0·0	1	1·0

*Each model contained smoking, age, asbestosis, and the exposure variable in step 4.
†The maximised log likelihood ratio χ^2 (LR χ^2) statistic at STEP 0 with only a constant in the model was −118·59 with 1 DF. The LR χ^2 reported is the improvement in the fit of the model to the data over the model fitted at the previous step.

Table 4 *Estimates of relative risk (odds ratios) for each of the four models with 95% confidence intervals (95% CI)*

	Model 1	*Model 2*	*Model 3*	*Model 4*
	Odds ratio (95% CI)	*Odds ratio (95% CI)*	*Odds ratio (95% CI)*	*Odds ratio (95% CI)*
Smoking:				
Never	1·0	1·0	1·0	1·0
Ex	3·06 (0·52–18·04)	2·45 (0·43–14·05)	2·60 (0·45–14·88)	2·63 (0·46–15·06)
Light	2·99 (0·47–18·88)	2·46 (0·40–15·02)	2·47 (0·40–15·22)	2·55 (0·42–15·66)
Moderate	3·39 (0·63–18·19)	2·43 (0·47–12·48)	2·51 (0·48–13·08)	2·57 (0·49–13·42)
Heavy	11·25 (2·01–62·98)	9·94 (1·83–53·91)	9·40 (1·72–51·36)	9·53 (1·74–52·16)
Age	1·07 (1·03–1·13)	1·06 (1·01–1·11)	1·07 (1·02–1·12)	1·07 (1·02–1·12)
Asbestosis:				
None	1·0	1·0	1·0	1·0
Slight	4·45 (1·64–12·08)	5·63 (2·15–14·73)	7·40 (2·98–18·40)	7·60 (3·06–18·84)
Moderate/pronounced	5·20 (1·60–16·88)	8·53 (2·92–24·91)	9·85 (3·28–29·58)	10·40 (3·57–30·32)
Exposure variable*	1·08 (1·02–1·14)	1·05 (0·99–1·11)	1·0	1·0

*Exposure variable refers to years of exposure to asbestos, residence time, fibre years, and residence TWD for models 1, 2, 3, and 4 respectively.

ing the likelihood of being a case of bronchial cancer was asbestosis with an improvement in the likelihood ratio χ^2 ($LR\chi^2$) of 30·1 with 2 DF ($p = 0·0001$) after adjusting for the effects of smoking habits (LR $\chi^2 = 10·1$; 4 DF, $p = 0·04$) and age (LR $\chi^2 = 14·83$; 1 DF, $p = 0·001$). In model 1 years of exposure to asbestos emerged as an additional contributor to the likelihood of being a case (LR $\chi^2 = 6·36$; 1 DF, $p = 0·01$). No other measurement of exposure emerged as an additional risk factor.

The pattern of odds ratios remained consistent for each of the four models (table 4). Raised odds ratios were found for heavy smokers, age, both categories of asbestosis, and years of exposure. In model 1, for example, the estimated increase in risk of developing bronchial cancer was 11·25 for heavy smoking (95% CI, 2·01; 63·0), for each increasing year of age 1·07 (1·03; 1·13), for slight asbestosis 4·45 (1·64; 12·08), moderate pronounced asbestosis 5·2 (1·60; 16·88), and for each additional year of exposure to asbestos 1·08 (1·02; 1·14). The latter extrapolates to 2·08 (1·20; 3·59) for every additional 10 years of exposure to asbestos.

The SPMRs shown in table 5 are calculated both for the 35 cases of bronchial cancer proved by necropsy and the 25 cases of bronchial cancer as certified on the death certificate.

Table 5 *SPMRs for the number of cases of bronchial cancers observed by grade of asbestosis*

Asbestosis	*No*	*Expected*	*Observed**	*SPMR*	*Observed†*	*SPMR*
None	302	12·4	11	88·7	8	64·5
Slight	69	3·6	15	416·7	11	305·6
Moderate/ pronounced	28	1·6	9	562·5	6	375·0

*Cases of bronchial cancer proved by necropsy.
†Cases of bronchial cancer as certified on death certificate.
SPMR = Standardised proportional mortality rates.

Discussion

This analysis indicates that of the variables of interest, the presence of asbestosis and indices of exposure (years of exposure, residence time, fibre years, and residence TWD), the presence of asbestosis was by far the most significant risk factor to being a case of bronchial cancer, $p < 0·0001$ (table 3).

The only index of exposure that remained significant after the effect of the presence of asbestosis had been taken into consideration was years of exposure $p = 0·01$ (table 3). The odds ratio, 1·08, was small but the 95% CI were narrow, 1·02–1·14 (table 4).

Cumulative asbestos respirable dust exposure expressed as fibre years had no significant effect and the effect of residence time ($p = 0·1$, OR 1·05 (0·99–1·11) remained doubtful.

Kipen *et al* recently reported that all 138 cases of lung cancer for whom they were able to obtain a tissue specimen had asbestosis on histology.[7] The cases arose out of the large prospective mortality study of asbestos insulation workers studied by Selikoff *et al*.[8] Unfortunately no information on duration or intensity of exposure was given in this paper but exposure was probably prolonged.

In rats Wagner *et al* found that there was a positive association between asbestosis and lung tumours in a large experiment in which the animals had been exposed to clouds of various mineralogical types of asbestos for periods varying from one day to two years.[9] The animals with tumours had significantly more asbestosis than those without ($p < 0·001$). Even rats with minimal or slight asbestosis had a significantly higher rate of tumours than those without asbestosis if they had survived at least 600 days. On the other hand, rats with no asbestosis had an incidence of tumours no higher than unexposed controls.

There is some evidence that the presence and

profusion of irregular opacities on the radiograph correlate with the risk of bronchial cancer, though there is probably still a small risk when the radiograph is normal.[10]

Liddell and McDonald have reported that men with 20 years or more employment in the lower dust concentrations showed no statistically significant excess mortality for any condition except pneumoconiosis and conclude that most but not necessarily all cases of lung cancer attributable to asbestos would show opacities before death.[11]

A histological diagnosis of asbestosis as presented in this paper should give a more accurate estimate of the association between exposure to asbestos, asbestosis, and bronchial cancer.

The SPMR for both the 35 cases proved by necropsy and the 25 cases certified as bronchial cancer on the death certificate show no excess bronchial cancer in the group without asbestosis whereas there is an excess in those with asbestosis. The excess increases with the severity of the asbestosis found at necropsy (table 5).

In conclusion this study suggests that asbestos caused bronchial cancer is almost always associated with some degree of histologically demonstrable asbestosis. It must be emphasised that these results should not affect compensation bodies dealing with living subjects exposed to asbestos as slight asbestosis is commonly, and moderate asbestosis occasionally, undetected radiologically.[12]

We thank Dr W P D Logan and Dr P A Hessel for advice on the analysis. We acknowledge the work of the pathologists of the National Centre for Occupational Health which generated the data analysed in this paper.

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CORRESPONDENCE

Relation between asbestosis and bronchial cancer in amphibole asbestos miners

Sir—Sluis-Cremer and Bezuidenhout (1989;46:537–40) present data on the relation between asbestosis and bronchial cancer in amphibole miners but analyse the effect of dose of asbestos only after allowing for the effect of asbestosis grade. Since the risk and severity of asbestosis are themselves dose related much of the effect of dose on the risk of cancer had already been allowed for by the analysis of the effect of asbestosis grade. Nevertheless, years of exposure, probably the most reliable measure of dose because it is known more accurately than intensity, still had a significant effect. This is consistent with the dose of asbestos rather than asbestosis being the major determinant of the risk of cancer.

It would be interesting to see the results of a further analysis of the data in which the various measures of dose were entered into the logistic regression before the asbestosis grade to determine the effect of asbestosis after the effect of dose of asbestos has been allowed for. To shed further light on the relation between asbestosis and bronchial cancer the ideal analysis would compare the incidence of cancer in subjects with and without asbestosis matched for dose of asbestos received. I wonder whether their data include sufficient subjects to attempt such an analysis?

Their analysis concerned subjects who had undergone necropsy, which occurred in a minority of deaths in the study population. The criteria for selection for necropsy were not mentioned. If necropsy had been more ; 103-ATC-13.1.90likely to be carried out in men with cancer if there had also been evidence of asbestosis during life, as has been the case in the United Kingdom until recently, this would have tended to augment the apparent effect of asbestosis on the risk of cancer. It is not indicated whether the presence of asbestosis was assessed without knowledge of whether or not cancer was present. Pathologists commonly look harder for asbestosis when they know bronchial cancer is present.

Table 2 of the paper shows that there were large standard deviations in the various measures of dose and suggests that subjects with only brief exposure were included. The observation that there appeared to be no excess risk of cancer in the group without asbestosis may indicate no more than that many of them had relatively slight exposure.

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Dr Sluis-Cremer and Mr Bezuidenhout reply:

We have carried out the two analyses suggested by Rudd. It must be mentioned, however, that what he first suggests is the assessment of the risk of developing bronchial cancer in the presence of asbestosis after controlling for the effect of the various measures of dose. In our paper we state our objective "... to determine if any parameter of exposure to asbestos dust exert any *additional* risk of developing bronchial cancer after allowing for the presence of asbestosis." After adjusting for the effects of smoking and age then entering the various measures of dose in separate analyses followed by asbestosis grade the latter still emerged as a significant risk factor for bronchial cancer. Admittedly, years of exposure accounted for most of the variation in model 1 (table 1) but notwithstanding this, the grade of asbestosis still emerged as a highly significant risk factor for bronchial cancer.

Following Rudd's next suggestion we were able to match to each of the 35 cases two to four referents with year of exposure within 20% of that of the respective case. A conditional logistic regression analysis was performed on the matched case-referent set of 157 subjects to assess the effect of asbestosis absent/present on risk of bronchial cancer after adjusting for the effects of age and smoking (table 2). The improvement in the fit of the model to the data with the introduction of asbestosis was significant (LR $\chi^2 = 5{\cdot}55$; 1 df, $p = 0{\cdot}02$) with the estimate of the relative risk by the odds ratio (OR) significant at 3·4 ($p = 0{\cdot}03$; 95% CI:1·1–10·46). As in the

Table 1 Goodness of fit χ^2 values for the stepwise unconditional logistic regression analysis

Model	Step	Term entered	Improvement in LR χ^2	Degrees of freedom	p Value
1	1	Smoking	10·13	4	0·04
	2	Age	14·83	1	0·0001
	3	Exposure (y)	25·44	1	<0·001
	4	Asbestosis	11·01	2	0·004
2	3	Residence time	12·23	1	0·0005
	4	Asbestosis	20·64	2	<0·0001
3	3	Fibre years	3·95	1	0·05
	4	Asbestosis	26·6	2	<0·0001
4	3	Residence time weighted dosage	1·65	1	0·20
	4	Asbestosis	28·44	2	<0·0001

Table 2 Goodness of fit χ^2 values for the stepwise conditional logistic regression analysis matching cases and referents by years exposure

Step	Term entered	Improvement in LR χ^2	Degrees of freedom	p Value
1	Smoking	9·29	4	0·054
2	Age	0·39	1	0·53
3	Asbestosis	5·55	1	0·018

unconditional logistic analysis in the published paper, heavy smoking emerged as a significant contributor to the risk of bronchial cancer (OR = 7·9; p = 0·02; 1·4–43·2).

The necropsy rate in the study population was low (37%) by South African standards; 85% in gold miners. The necropsy cases were not selected by any authorities but by the doctors and family of the dead men in the hope of obtaining compensation. Men with advanced disease would probably have already obtained maximum compensation and there was thus no need for necropsy. The families of workers with short or forgotten service or ignorant of the regulations may not have insisted on necropsy. Lung cancers if diagnosed in life would have obtained maximum compensation. We agree that there are probably selection factors for necropsy of which we are ignorant.

The mean net duration of exposure of cases of cancer without asbestosis was six years and their referents without cancer or asbestosis was eight years—this is hardly "slight" exposure. Among those with asbestosis, patients with cancer had 13 years of exposure and their referents without cancer 14 years.