

Radiographic abnormalities and mortality in subjects with exposure to crocidolite

Nicholas H de Klerk, A William Musk, William O C M Cookson, John J Glancy, Michael S T Hobbs

Abstract

Plain chest radiographs from a one in six random sample of the workforce of the asbestos industry at Wittenoom, Western Australia between 1943 and 1966 have been classified for degree of profusion and pleural thickening by two independent observers according to the 1980 UICC-ILO Classification of Radiographs for the pneumoconioses to clarify the effect of degree of radiological abnormality on survival. A total of 1106 subjects were selected. Each subject's age, cumulative exposure to crocidolite, and time since first exposure were determined from employment records, the results of a survey of airborne concentrations of fibres $>5 \mu$ in length conducted in 1966, and an exposure rating by an industrial hygienist and an ex-manager of the mine and mill at Wittenoom. By the end of 1986 193 subjects had died. Conditional logistic regression was used to model the relative risk of death in five separate case-control analyses in which the outcomes were deaths from: (1) all causes, (2) malignant mesothelioma, (3) lung cancer, (4) asbestosis, and (5) other causes excluding cancer and asbestosis. Up to 20 controls per case were randomly chosen from all men of the same age who were not known to have died before the date of death of the index case. After adjustment for exposure and time since first exposure, there were significant and independent effects of radiographic profusion and pleural thickening on all cause mortality. The effect of profusion was largely a result of the effect on mortality from malignant

mesothelioma and asbestosis but not lung cancer. The effect of pleural thickening was greatest on mortality from other causes, mainly ischaemic heart disease. This study has shown that degree of radiographic abnormality has an independent effect on mortality from malignant mesothelioma, asbestosis, and all causes even after allowing for the effects of age, degree of exposure, and time since first exposure.

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Subjects with exposure to asbestos with or without pneumoconiosis have been shown to be subject to excessive mortality from malignant and non-malignant diseases of the respiratory and gastrointestinal tracts.¹⁻³ Incidence and mortality for some of these diseases have been related to the degree of exposure and the time since exposure to asbestos.⁴⁻⁶

A previous study of crocidolite workers from Wittenoom Gorge in Western Australia who had applied for compensation for asbestosis showed that mortality was also related to the profusion of radiographic abnormalities on the plain chest radiograph⁷ and there have been similar findings elsewhere in workers exposed to chrysotile.⁸ More recently some studies have suggested that asbestosis is responsible for the excess of cases of lung cancer in asbestos workers and have shown significant effects of exposure to asbestos on lung cancer only in those with asbestosis diagnosed either radiographically⁹ or histopathologically.¹⁰

The study among Wittenoom workers applying for compensation⁷ also showed an effect of amount of exposure on severity of radiographic profusion but survival in this group of workers was not significantly related to cumulative exposure to asbestos. This raised the possibility of bias introduced into the study by the subjects' selection on the basis of a claim for compensation. To clarify the effects of age, exposure, and radiographic abnormalities on the mortality of subjects who have been exposed to asbestos but have not necessarily sought compensation we have taken a random sample of the entire

Department of Respiratory Medicine
A W Musk, W O C M Cookson
Department of Diagnostic Radiology, Sir Charles
Gairdner Hospital, Nedlands, Western Australia
J J Glancy
Department of Public Health, University of Western
Australia
N H de Klerk, M S T Hobbs

workforce of Wittenoom between 1943 and 1966 and examined their survival experience in relation to these variables.

Subjects

There were about 7000 workers employed in the crocidolite industry at Wittenoom Gorge between 1943 until 1966. The employment records of the Australian Blue Asbestos Company (ABA) have been retained and form the basis of a continuing follow up study of morbidity and mortality in the workforce that has been conducted since 1975.^{3 11 12} This study has provided information on vital status and cause of death of most of the employees, about 70% of whom are known to be dead or alive and living in Australia. Quantitative estimates of exposure to crocidolite of all subjects in the industry have been made possible by the existence of records of fibre counting in the industry.¹³ Compulsory chest x ray films of workers entering the mining industry and periodically while they remain in it, an active tuberculosis control programme in the State in the past, doctors' referrals or voluntary presentation for free chest radiographs, and a policy of indefinite preservation of all films have led to an invaluable collection of serial chest x ray films at the Perth Chest Clinic.

A one in six random sample of all male Wittenoom workers (including those who had sought compensation) was selected and attempts were made to obtain all plain chest radiographs on them held in the Perth teaching hospitals or the Perth Chest Clinic. A total of 1106 men was selected. Radiographs were retrieved for 921 men and of these 740 had radiographs taken at or after commencing employment at Wittenoom. Four hundred and sixty seven had x ray films taken more than six months after they had started work at Wittenoom.

Methods

All radiographs were classified independently by two observers (A W M and J J G) according to the 1980 International Labour Office (ILO) classification of radiographs for pneumoconiosis.¹⁴

The duration and place of work at Wittenoom for each subject have been documented.³

The concentrations of airborne respirable fibres greater than 5μ in length in various workplaces were measured in 1966.¹³ This information permitted an estimate of the cumulative exposure for each subject in fibres/ml-years (f/ml-years).^{3 12}

Demographic and basic exposure data were obtained from employment records supplemented, when incomplete, by records of the Perth Chest Clinic, which took compulsory pre-employment and periodic subsequent chest x ray film examinations of the men (both miners and millers), and by records of the Western Australian Mineworkers

Relief Fund, a compulsory benevolent fund to which the company paid monthly subscriptions for each employee. These data included date of birth, nationality, and date and occupation at the beginning and date of end of each period of employment. Vital status and date and cause of death were determined as part of the mortality study of the total cohort up to the end of 1986.¹²

Five separate case-control analyses were performed. The outcomes in the five sets of cases were: (1) all causes, (2) malignant mesothelioma, (3) cancer of the trachea, bronchus, and lung, (4) asbestosis, and (5) all causes excluding cancer and asbestosis. Controls were chosen from all men of exactly the same age who were not known to have died before the date of death of the index case. Up to 20 controls, if possible, were randomly chosen. If there were fewer than 20 men eligible to be selected then all eligible men were chosen as controls.

Conditional logistic regression analyses¹⁵ were used to model the relative risk of death from each of the above causes with the computer program Egret.¹⁶ The covariates considered were (1) log (cumulative exposure + 1), (2) years since first employed, and (3) level of radiographic abnormality, either in minor ILO categories for profusion of small opacities or in categories of thickness and extent for pleural thickening.

Scores on x ray films were grouped according to time before the death of the case. Thus each person's x ray film history was coded as: presence or absence of an x ray film and their latest level of profusion and thickening in the periods before the death of the case of (1) less than or equal to one year (any signs in this period were considered to be early presence of disease rather than true precursors of disease and were ignored), (2) two to five years ago, (3) six to 10 years ago, (4) 11 to 20 years ago, (5) 21 to 30 years ago, and (6) 31 or more years ago. Analyses were done separately for each period and were restricted to those subjects who had had an x ray film during that period. The effects of the radiographic scores were examined alone, and then after adjustment for exposure.

As an added comparison with the previous study on compensated subjects alone,⁷ the effect of exposure on the level of radiographic abnormality on the final film for each person was examined with multiple regression. This analysis was restricted to the 467 men with x ray films taken more than six months after commencing employment at Wittenoom.

Results

Out of a total of 193 deaths among the 1106 selected subjects there were 12 from mesothelioma, 19 from lung cancer, 24 from other cancers, and nine

Table 1 Causes of death in 1106 men

Cause	No of deaths
Malignant mesothelioma	12
Lung cancer	19
Stomach cancer	2
Other cancer	22
Pneumoconiosis	9
All other causes	129

from asbestosis (table 1). By comparison with the total cohort of Wittenoom workers,¹² there were fewer deaths than expected (on a proportional basis) from every cause examined, although exposure to asbestos was similar (table 2).

After adjustment for cumulative exposure, there was a significant effect of *x* ray film profusion on mortality from all causes (table 3). The further back in time the *x* ray films were taken, the lesser the effect, which was not statistically significant more than 20 years previously. A similar effect was found for pleural thickening but this only became non-significant more than 30 years previously.

On examination of the effects of the radiographic variables on death from separate causes it was clear that the effect of profusion was largely on mortality from mesothelioma and asbestosis whereas pleural thickening seemed to be a risk factor for death from ischaemic heart disease, which formed the largest proportion of deaths from other causes (table 3). There was no significant effect of either exposure to asbestos or radiographic abnormality on mortality from lung cancer. There was an additional logarithmic decrease in the mortality from other causes with time from first exposure.

Figures 1-3 show comparative sizes of the different estimated effects of both radiographic signs and exposure to asbestos on the different causes of death. The strongest effects of both factors were on deaths from asbestosis and mesothelioma.

Age at first exposure, time since first exposure, and the log of cumulative exposure were all significant predictors of both radiographic profusion of small opacities and diffuse pleural thickening on the subjects' final *x* ray films (table 4). The coefficients for time from first exposure for both types of abnormality were more than double the respective age at

Table 2 Exposure to asbestos (geometric means) and cause of death

	Cumulative (f/ml-years)	Intensity (f/ml)	Duration (days)
Lung cancer	11	17	223
Mesothelioma	44	24	660
Asbestosis	84	30	1032
Remainder	7	14	164
Controls*	6	13	153

*Mean of the mean of all sets of controls.

Table 3 Effect of radiographic abnormality (two to five years earlier) and exposure on mortality from various causes (non-significant ($p > 0.3$) variables omitted)

	Relative Risk (95% CI)	<i>p</i> Value*
All causes:		
Profusion (/minor ILO category)	1.3 (1.1-1.5)	0.006
Pleural thickening (25% increase)	1.3 (1.1-1.5)	0.002
Log (cumulative exposure; f/ml-years)	1.2 (1.1-1.3)	<0.001
Log (time from first exposure; y)	0.5 (0.4-0.6)	0.004
Malignant mesothelioma:		
Profusion	1.9 (1.3-2.9)	0.002
Log (cumulative exposure)	2.5 (1.6-4.0)	<0.001
Lung cancer:		
Log (cumulative exposure)	1.2 (0.9-1.6)	0.12
Asbestosis:		
Profusion	1.6 (1.1-2.3)	0.02
Log (cumulative exposure)	4.0 (1.8-8.8)	<0.001
Other causes:		
Pleural thickening	1.5 (1.3-1.8)	<0.001
Log (time from first exposure)	0.5 (0.3-0.7)	0.002

**p* Value for removal from full model.

first exposure coefficients. Replacing the two time terms by age at *x* ray film (the sum of age at first exposure and time from first exposure) resulted in a significantly worse fit to the data.

Discussion

This study has shown that in a sample of randomly selected subjects with exposure to crocidolite at Wittenoom, after adjusting for the effects of age, mortality from all causes was determined by the level of both pleural and parenchymal radiographic abnormality, the cumulative exposure to asbestos, and the time from first starting work. Both types of radiographic abnormality had their maximum effect on mortality between two and five years after the *x* ray film. Also, the degree of both types of abnormality was also dependent on the cumulative exposure to asbestos, age at first exposure, and time

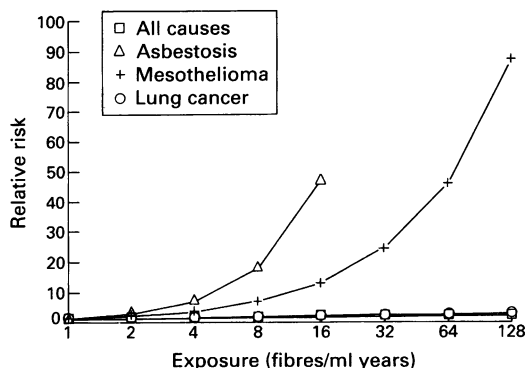


Figure 1 Estimated change in relative risk of death from asbestosis, mesothelioma, lung cancer, and all causes for levels of cumulative exposure to crocidolite.

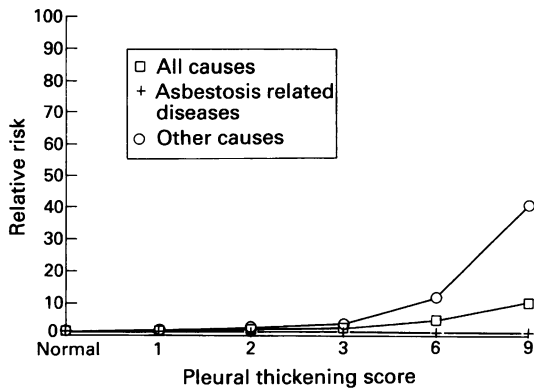


Figure 2 Estimated change in relative risk of death from asbestosis, mesothelioma, lung cancer, and all causes for levels of ILO profusion of small opacities.

from first exposure. The difference in the regression coefficients of age at first exposure and time from first exposure associated with both abnormalities showed that the effect of time from first exposure was unlikely to be just an effect of age.

Exposure to asbestos had a strong effect on mortality from mesothelioma and asbestosis even after adjustment for degree of radiographic profusion and in turn, mortality from malignant mesothelioma and asbestosis were related to profusion of small opacities in the two to five years before death.

There was no significant effect of any measure of exposure to asbestos on mortality from lung cancer; neither was there a significant effect of any radiographic measure of pleural or parenchymal fibrosis. The relative risk of mortality from lung cancer for log (cumulative exposure) of 1.2 was not, however, greatly different from the 1.4 found

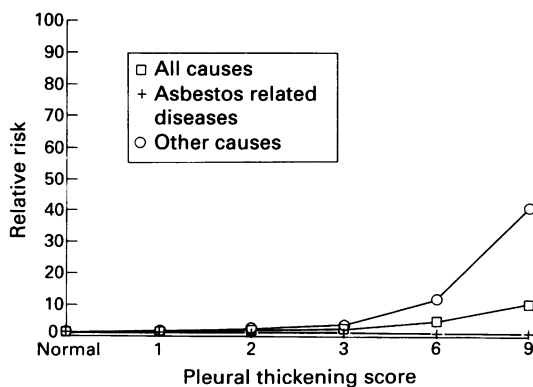


Figure 3 Estimated change in relative risk of death from all causes, asbestos related diseases (mesothelioma, asbestosis, and lung cancer), and other causes for levels of categories of thickness and extent of diffuse pleural thickening.

Table 4 Effect of exposure to asbestos on abnormalities on final x ray films

	<i>b</i> *	(95% CI)	<i>r</i> ²
Level of profusion:			
Log(cumulative exposure)	0.13	(0.05-0.21)	0.10
Time since starting work(y)	0.04	(0.03-0.05)	
Age at starting work	0.017	(0.002-0.033)	
Level of thickening:			
Log(cumulative exposure)	0.10	(0.02-0.18)	0.19
Time since starting work(y)	0.07	(0.06-0.08)	
Age at starting work	0.016	(0.000-0.032)	

*Increase in minor ILO category for profusion and in category of thickness and extent for pleural thickening per unit increase in exposure variable.

in a more powerful study among Wittenoom workers with known smoking habits.¹⁷ It has been estimated that smoking caused 71% of the 132 deaths from lung cancer among men in the whole Wittenoom cohort.¹⁸ Given the small numbers of lung cancers in this random sample, this study had little power to detect an effect of either exposure or radiographic abnormality and does not therefore contribute to understanding the relations between exposure to asbestos, asbestosis, and lung cancer.

Pleural thickening had no effect on mortality from diseases related to asbestos but seemed to influence deaths from other causes (particularly ischaemic heart disease). This finding suggests a chance association although it is now accepted that pleural thickening is not totally benign¹⁹ and poor lung function has often been associated with mortality from cardiovascular disease.²⁰ The significant reduction in mortality from causes other than those related to asbestos with time from first exposure was probably due to the occurrence of undetected deaths, which has been shown to be related to age in other analyses.²¹

The results of this study differ from those found in a previous study in subjects from Wittenoom who were selected because they had applied for pneumoconiosis compensation.⁷ In compensated men whose exposures were all relatively high, the degree of exposure had no independent effect on survival whereas the effect of exposure on profusion level was more than twice that found in this random sample. Since the first study was completed all subjects have had their estimated airborne exposures re-evaluated³ and this could contribute to these differences especially as in the previous study there was also a large and significant effect of working in the mill on mortality from asbestosis and all causes that was not present in this study.

The significant effect of exposure to asbestos on pleural thickening also contrasts with that found previously in a study of heavily exposed men applying for compensation.²² In that study no exposure related variable had any effect on incidence or progression of pleural thickening except in the period

five to 15 years after first exposure. This could again be due to the greater range of exposures over the whole cohort.

This study shows that the degree of profusion of small irregular opacities on plain chest x ray film has an independent effect on mortality from malignant mesothelioma and asbestosis even after allowing for the effects of age, degree of exposure, and time since exposure.

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Requests for reprints to: Nicholas de Klerk, Department of Public Health, University of Western Australia, Nedlands, 6009, Western Australia.

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