

ORIGINAL ARTICLE

The effect of asbestosis on lung cancer risk beyond the dose related effect of asbestos alone

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Aims: To determine if the presence of asbestosis is a prerequisite for lung cancer in subjects with known exposure to blue asbestos (crocidolite).

Methods: Former workers and residents of Wittenoom with known amounts of asbestos exposure (duration, intensity, and time since first exposure), current chest x ray and smoking information, participating in a cancer prevention programme (n = 1988) were studied. The first plain chest radiograph taken at the time of recruitment into the cancer prevention programme was examined for radiographic evidence of asbestosis according to the UICC (ILO) classification. Cox proportional hazards modelling was used to relate asbestosis, asbestos exposure, and lung cancer.

Results: Between 1990 and 2002 there were 58 cases of lung cancer. Thirty six per cent of cases had radiographic evidence of asbestosis compared to 12% of study participants. Smoking status was the strongest predictor of lung cancer, with current smokers (OR = 26.5, 95% CI 3.5 to 198) having the greatest risk. Radiographic asbestosis (OR = 1.94, 95% CI 1.09 to 3.46) and asbestos exposure (OR = 1.21 per f/ml-year, 95% CI 1.02 to 1.42) were significantly associated with an increased risk of lung cancer. There was an increased risk of lung cancer with increasing exposure in those without asbestosis.

Conclusion: In this cohort of former workers and residents of Wittenoom, asbestosis is not a mandatory precursor for asbestos related lung cancer. These findings support the hypothesis that it is the asbestos fibres per se that cause lung cancer, which can develop with or without the presence of asbestosis.

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Exposure to blue asbestos (crocidolite) increases the risk of lung cancer.¹⁻³ Less certain is our understanding of the role of asbestosis (pulmonary fibrosis) in the pathogenesis of lung cancer in people exposed to asbestos. Three studies have suggested that asbestosis is a necessary precursor to lung cancer,⁴⁻⁶ but these studies have been criticised for their methods,^{6,7} and their findings have not been replicated elsewhere.⁸⁻¹⁰ Statistical co-linearity in the dose-response relations between lung cancer and exposure and asbestosis and exposure are suggested to explain the relation between asbestosis and lung cancer.¹⁰ McDonald⁷ concluded that on balance, "present evidence suggests that a direct link exists between asbestos exposure and lung cancer". In the medico-legal setting, compensation awards for lung cancer made to persons exposed to asbestos may be determined by the presence of asbestosis. In Australia, the presence of asbestosis is not necessary for a compensation award for asbestos related lung cancer in either Western Australia or New South Wales.

Crocidolite was mined at Wittenoom Gorge in the remote Pilbara region of Western Australia between 1943 and 1966.¹¹ During that time 6493 men and 415 women were known from employment records to have been employed in either the mining or milling process of the now defunct Australian Blue Asbestos Company.¹² A further 4890 are recorded to have lived and worked in the town and surrounding settlements.¹³⁻¹⁶ These two cohorts have been followed up since 1975 to document the epidemiology of asbestos related diseases.¹⁷⁻¹⁸ Cohort members are unique in that their exposures were almost exclusively to crocidolite as few people had worked or went on to work in other jobs where they were exposed to other forms of asbestos. The exposures have been extensively documented,¹²⁻¹⁵ and the rates of asbestos related diseases in both the cohorts carefully followed.

We aimed to examine the effect on lung cancer risk of having asbestosis, beyond the dose related effect of asbestos alone among former workers and residents of the crocidolite mining and milling town of Wittenoom participating in a cancer prevention programme.

METHODS

Because of the projected incidence of mesothelioma in the former workforce of Wittenoom,¹⁹⁻²⁰ in early 1990 all surviving former workers who had replied to a questionnaire on smoking in 1979 (n = 2373) were invited to take part in a cancer prevention programme to examine the efficacy of beta carotene and retinol in reducing the risk of malignant mesothelioma, lung cancer, and other cancers.^{21,22} Former residents of Wittenoom were not actively recruited into the programme but were included when approached to do so. A total of 1196 former workers (50% of workers who replied to smoking questionnaire) and 792 former residents (17% of former residents' cohort) joined the programme between 1990 and 1996, most in the first year. Standard posterior-anterior plain chest radiography was carried out on all participants at the time of joining the programme. Subjects were randomly assigned to take either 30 mg synthetic all-trans beta carotene or 25 000 IU retinyl palmitate daily, except former Wittenoom residents, women of childbearing age, and subjects with abnormal liver function who were randomised to either 0.75 mg or 30 mg beta carotene daily.²¹ Results after five years showed that the risk of mesothelioma was significantly lower in participants assigned to receive retinol supplementation, but there was no effect associated with beta carotene.^{21,22} Supplementation with beta carotene was ceased in 1997 after this result and the results of other

Abbreviations: CI, confidence interval; HR, hazard ratio; OR, odds ratio

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trials finding increased rates of lung cancer among smokers taking similar doses of synthetic beta carotene.²³ Thereafter all participants were assigned to 25 000 IU retinol/day, except women of childbearing age and participants with abnormal liver function who were offered 5000 IU retinol daily. All participants are reviewed annually and the results of liver function test performed to identify possible vitamin A toxicity.

Asbestosis was classified in accordance with the UICC/ILO classification²⁴ using the plain chest radiograph taken at the first visit ($n = 1988$). Asbestosis was recorded when the profusion of small irregular opacities was $\geq 1/0$ in one zone bilaterally. All films were read in duplicate or triplicate by trained and experienced readers. Analysis was done using one reader. This reader was chosen as the one who, when three readers were available, agreed most closely with the median reading of all three. Smoking history was classified as never, past, and current based on the information given at the first visit.

Case ascertainment

Participants have been followed up actively through attendance at the clinic each year and passively through death and cancer registries. Incident cases of lung cancer were determined from the Western Australian Cancer Registry up to September 2002 and the National Cancer Clearing House to September 2000. Lung cancer was identified using ICD0, 2nd edition, categories C33.9-C34.9. Subjects were censored at their date of diagnosis of lung cancer, date of death, September 2000 for non-Western Australian residents, or September 2002 for West Australian residents, whichever was earliest.

Ethics approval was obtained from the Human Research Ethics Committee of the University of Western Australia.

Asbestos exposure assessment

Workers

Periodically between 1948 and 1958, measurements of dust concentrations were taken in the mine and the mill, by the Mines Department of Western Australia using a konimeter,¹² and a survey of fibre counts using a Casella long running thermal precipitator was performed across the industry in 1966.¹³ These measurements and the employment records provided by the Australian Blue Asbestos Company, supplemented by records of contributions to a Mine Workers Relief Fund for workers prior to 1943 enabled the calculation of each former asbestos miner or miller's cumulative exposure in fibre-years per ml, by adding over all their jobs the product of their estimated fibre concentration and the length of time in the job.

Residents

Based on surveys of fibre counts performed periodically by the Health Department of Western Australia and the Mines Department of Western Australia, former residents of the township of Wittenoom not working directly with asbestos were assigned an intensity of exposure of 1.0 fibres ($>5 \mu$ long) per millilitre of air (f/ml) from 1943 to 1957 (when a new mill was commissioned and the town was moved), and then 0.5 f/ml between 1958 and 1966, when the mining operations ceased.^{25, 26} Interpolation between surveys using personal monitors assigned exposures from 0.5 f/ml in 1966 to 0.010 f/ml in 1992. Duration of residence was extracted from a questionnaire sent to the subject, or was taken as those found in various documentary sources: state primary school records, admission and outpatient records from the hospital, the State Electoral Roll for the Pilbara district, and information supplied by other participants' questionnaire

responses. Cumulative exposure (fibre-years per ml) was calculated from the intensity and duration of exposure.^{25, 27}

Former workers who joined the cancer prevention programme were similar in age (57, range 40-84) than those former workers who did not join the programme (58, range 40-85) and in their intensity of asbestos exposure (24 f/ml, range 1-130; and 23 f/ml, range 1-130, respectively).²¹ Former residents of Wittenoom who joined the programme were similar in age (mean 43, SD 13.6) to those who did not join (mean 45, SD 17.3) and in their intensity of asbestos exposure (median (range) 2.10 f/ml (2.01-2.93) and 2.09 f/ml (1.53-2.68) respectively). Those former residents who joined the programme had spent more time at Wittenoom (730 days (335-1461)) compared to those who did not join the programme (457 days (183-1126)).

Statistical analysis

Asbestos exposure variables were positively skewed and so were transformed to their natural logs. Cox proportional hazards modelled the risk of lung cancer incidence, considering the covariates of cumulative asbestos exposure, smoking status, age at the start of the study, and the presence of profusion of small irregular opacities $\geq 1/0$. A test for interaction was used to examine the slope of the dose-response relation for lung cancer and cumulative asbestos exposure between those with asbestosis and those without it at the start of the study. The analysis was undertaken on all participants and then repeated on those without asbestosis at the start of the study separately. Insufficient numbers were available to examine those with asbestosis at the start of the study separately. All analysis was undertaken using Stata 8.0.²⁸

RESULTS

Between 1990 and 2002 there were 52 incident cases of lung cancer in men and six in women (table 1). Cases had a greater intensity of asbestos exposure and greater cumulative exposure than the remainder of the cohort. Twelve per cent of participants had radiographic evidence of asbestosis (table 1). The prevalence of asbestosis on the plain chest radiograph was much greater for cases than non-cases.

Smoking was the strongest predictor of lung cancer and current smokers had the greatest risk (table 2). Over one third of cases had radiographic asbestosis compared with one tenth of the non-cases. After adjusting for smoking and age at the start of the study, both cumulative asbestos exposure and radiographic asbestosis significantly increased the risk of lung cancer. The interaction between cumulative asbestos exposure and asbestosis was not significant (HR = 0.82, 95% CI 0.59 to 1.13, $p = 0.23$).

The models were repeated on those without asbestosis at the start of the study. Cumulative asbestos exposure (HR = 1.31 per log f/ml-y, 95% CI 1.06 to 1.62), ex-smoking (HR = 7.07, 95% CI 0.93 to 53.65), and current smoking (HR = 21.8, 95% CI 2.85 to 166.8) remained significantly associated with an increased risk of lung cancer in those subjects who did not have evidence of radiographic asbestosis at the start of the study. Being a resident (HR = 0.51, 95% CI 0.16 to 1.63) or male (HR = 1.12, 95% CI 0.35 to 3.57) were not associated with an increased risk of lung cancer in those subjects who did not have asbestosis at the start of the study.

DISCUSSION

In this cohort of former workers and residents of Wittenoom, subjects with lung cancer had a greater intensity of exposure to asbestos than did non-cases. The presence of asbestosis further increased the risk of lung cancer beyond the dose-response effect of asbestos exposure alone, but this study also shows that the presence of radiographic asbestosis is not a

mandatory precursor for lung cancer in this cohort. The test for interaction between cumulative asbestos exposure and asbestosis showed there was no difference in the slope of the dose-response relation between those with or without asbestosis. Cumulative asbestos exposure was significantly associated with an increased risk of lung cancer in persons without asbestosis at the start of the study.

The particular strength of this study in comparison with others that have examined this issue is the availability of quantified asbestos exposure information to a single known type of asbestos fibre: workers and residents of Wittenoom were exposed almost exclusively to crocidolite. This information enabled us to examine the effect of asbestosis on lung cancer, taking asbestos exposure into account. Wilkinson and colleagues²⁹ examined chest radiographs for asbestosis and histories to determine asbestos exposure of 271 lung cancer cases and 678 controls. After adjusting for age, sex, smoking history, and place of referral, the group with asbestosis showed an OR of 2.03 (95% CI 1.00 to 4.13), while those without asbestosis had an OR of 1.56 (95% CI 1.02 to 2.39). The present study expands on this work because we examined the effect of asbestosis on lung cancer, adjusting for quantified levels of asbestos exposure, rather than examining asbestos exposure categorised as definite, probable, possible, or unlikely.

In the current study we found asbestos exposure (cumulative exposure) had an independent effect on lung cancer

after adjusting for smoking status, age, and asbestosis as categorised by the UICC/ILO classification. Sluis-Cremer and colleagues⁶ did not find an excess of lung cancer mortality among 302 men exposed to asbestos but without asbestosis. However they did find that duration of exposure, the most accurately measured exposure variable,⁶ was independently associated with lung cancer (OR = 1.08, 95% CI 1.02 to 1.14) after adjusting for smoking status, age, and grade of asbestosis.

Our findings differ from those of Hughes and Weill⁷ who examined mortality among 839 male manufacturers of asbestos cement products and found no increase in lung cancer risk with increasing exposure among workers without radiographically detectable lung fibrosis. This study had a low power to detect a lower risk of lung cancer in subjects without asbestosis.⁶ They report 26 deaths from respiratory malignancy, 10 of which did not have asbestosis. In contrast we report 58 incident cases of lung cancer, 37 of whom did not have radiographically defined asbestosis. A further strength of our study is a greater length of follow up after first exposure to asbestos, which was on average 31 years prior to joining the cancer prevention programme, compared with a mean of 24.3 years (SD 4.3) for men with the greatest cumulative exposure in the study of Hughes and Weill.

As would be expected, the present study shows that current and past smokers have a much greater risk of lung cancer compared to never smokers, after adjusting for both

Table 2. Relative risk of lung cancer from exposure to asbestos (fibres/m³-year) and asbestosis

	Relative risk	95% CI	P-value	Relative risk	95% CI	P-value
Non-smoker	1.00			1.00		
Past smoker	18.1 (2.48 to 132.5)		0.004	9.53 (1.28 to 70.3)		0.027
Current smoker	30.1 (4.06 to 223.7)		0.001	26.5 (3.54 to 198.5)		0.001
Asbestosis	4.71 (2.72 to 8.14)		0.002	3.24 (1.09 to 9.46)		0.035
Age at start of study	1.08 (1.05 to 1.11)		0.000	1.07 (1.04 to 1.11)		0.000
Male	4.09 (1.33 to 10.3)		0.009	1.24 (0.41 to 3.75)		0.701
Ex-resident	0.14 (0.04 to 0.35)		0.000	0.49 (0.16 to 1.48)		0.208
Cumulative asbestos exposure (fibre-years)	1.24 (1.22 to 1.25)		0.000	1.21 (1.01 to 1.42)		0.026

*Adjusted for all covariates.

asbestos exposure and asbestosis. We are currently addressing this issue in the Wittenoom workers cohort in more detail and hope to have the results published soon.

One way of assessing if asbestosis is a necessary precursor for lung cancer in persons exposed to asbestos is to examine if there is, a significant statistical interaction between asbestos exposure and asbestosis in their association with lung cancer. This question has not previously been answered by studies examining this topic.²² We found no difference in the effect of cumulative asbestos exposure on lung cancer in those with asbestosis and those without, indicating that the slope of the dose-response relation (between asbestos exposure and lung cancer) is not different between those with asbestosis and those without. This provides further evidence against the hypothesis that lung cancer is necessarily preceded by asbestosis in persons exposed to asbestos. We also repeated our models on those without asbestosis at the start of the study separately and found again that cumulative asbestos exposure was related to an increased risk of lung cancer in persons without radiographic evidence of asbestosis.

The estimates of asbestos exposure in the Wittenoom cohorts have been criticised for being underestimates of the true exposure.²⁰ We have validated these estimates as internally valid by showing an agreement with lung fibre burdens,²¹ and a clear relation between all asbestos related diseases and dose-response has been repeatedly documented within the cohort.^{12,18,23} In a review of several studies assessing asbestos exposure and lung cancer risk, Hodgson and Darnton found the Wittenoom exposures comparable to exposures reported from other crocidolite mines, and in addition found the lung cancer risk (R_L) similar to that from other studies.²⁴ We accept that our exposure estimates are possibly underestimates, given the paucity of the dust measurements collected at Wittenoom, but recognising their internal validity are confident of using them as a measure of quantified asbestos exposure.

In the present study we found that the relative risk of lung cancer was higher in former Wittenoom workers and ex-residents with asbestosis than those without asbestosis, even after adjusting for the amount of asbestos exposure. A possible explanation for this excess risk is that the fibrosis itself is causing some action over and above the dose-response effect of the asbestos exposure.⁴ Greater exposure to asbestos is one other possible explanation for this excess risk. It is possible that any underestimation of asbestos exposure in this cohort is greatest in those with heavier exposure. Therefore the presence of asbestosis may be a marker of heavy asbestos exposure, rather than being causal of lung cancer itself.

The relative risk of lung cancer in former Wittenoom residents was half that of the former miners and millers. This ratio is consistent with that found between former residents and workers for mesothelioma, where the mesothelioma rate was about half for the former residents than workers in each exposure category.²⁵ The asbestos exposure assessment for residents may give higher exposures compared to workers with equivalent exposures. The data available for estimating asbestos exposure was of a different form for residents and workers, as described in the methods section, so it is perhaps not surprising that there is a differential effect.

Former workers and residents who participated in the vitamin A cancer prevention programme were younger and had higher asbestos exposure than those who were invited but who did not join. In this study we have done a within group analysis, assessing those with and without asbestosis as determined by radiological examination. Therefore the higher exposure estimates and younger age of our study

participants would not unduly influence this study's findings.

In this study of former workers and residents of the township of Wittenoom, the presence of asbestosis is not a necessary precursor for lung cancer. This study provides further evidence to support the hypothesis that it is the asbestos fibres per se that cause lung cancer in persons exposed to asbestos. However, the presence of asbestosis is also associated with an increased risk of lung cancer which may be due to some action of the fibrosis itself, but in this study this excess risk may also be due to an underestimate of asbestos exposure.

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