Effects of asbestos and smoking on gas diffusion in people exposed to crocidolite

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ABSTRACT

Objective: To examine the effects of asbestos exposure and tobacco smoking on the level and rate of change of the diffusing capacity of the lung for carbon monoxide (DLCO).

Design and participants: A cohort study of 934 people (including both mine workers and town residents) exposed to crocidolite (blue asbestos) at the asbestos mines and in the town of Wittenoom, Western Australia, between 1943 and 1966. DLCO measurements were taken during a follow-up period from 1992 to 2002.

Main outcome measures: Baseline levels of DLCO and change in levels over time.

Results: 2980 DLCO measurements were done on 934 people (of whom 818 were men and 724 were workers) who underwent a median of 2 (range, 1–17) measurements during the follow-up period. Radiographic asbestosis at baseline and asbestos exposure at a younger age were associated with lower DLCO values. The average rate of decline in DLCO was 0.33 (95% CI, 0.31–0.35) units per year, plus an additional decrement of 0.22 (95% CI, 0.12–0.32) units per year if the participant had radiographic asbestosis at the beginning of the follow-up period. Compared with never-smokers, current smokers and ex-smokers had lower DLCO at baseline, but smoking status did not affect the change in DLCO during the follow-up period.

Conclusions: Our results confirm a continuous deleterious effect of crocidolite on DLCO, especially on people with asbestosis. Smoking was associated with lower DLCO levels, but was not a significant predictor of rate of change in DLCO. Smoking status did not affect the relationships between crocidolite exposure and the level or rate of change of DLCO in this population.

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Exposure to asbestos causes not only cancers and frank asbestosis, but also more subtle changes in the structure and function of the lungs. Thickening of the alveolar-capillary membrane and fibrosis of the interstitium impair oxygen transport and reduce the compliance of the lungs.[1,2] Further, some reports have suggested a positive interaction between smoking and asbestos exposure on the development of interstitial fibrosis.[3,4]

The single-breath carbon monoxide diffusing capacity (DLCO) test is clinically useful in diagnosing pulmonary vascular and interstitial lung diseases and in detecting emphysema. The measurement of DLCO is determined by the diffusing capacity of the alveolar-capillary membrane and the volume of blood in the alveolar capillaries, the former being predominantly affected by diffuse interstitial pulmonary fibrosis (as seen in asbestosis).[2,5] The DLCO measurement is not substantially influenced by airway calibre. It is therefore an easy, non-invasive means of examining the integrity of the lung parenchyma in vivo and of monitoring the course of obstructive and restrictive lung diseases. Previous cross-sectional studies have shown that asbestos exposure reduces DLCO.[6,7] In our study, we analysed the effects of crocidolite (blue asbestos) and tobacco smoking on changes in DLCO over time. To our knowledge, this is the first longitudinal study evaluating interactions between the effect of asbestos and smoking on gas diffusion.

METHODS

Participants

Wittenoom, in Western Australia, was the site of a crocidolite asbestos mine that was active between 1943 and 1966. During that time, about 7000 people worked in the mines ("workers") and about 5000 additional people lived in the nearby town ("residents").

Workers and residents have been followed up since 1979.[8,9] In 1990, former workers and residents were invited to participate in a program of vitamin A supplementation (in the form of retinol or β-carotene) in an attempt to reduce the incidence of cancer in this group. About 3000 workers and residents have participated in the program, which is discussed in more detail elsewhere.[10-12]

Although the main aim of the program was to reduce cancer rates, there was also interest in whether vitamin A supplements would improve lung function. Consequently, spirometry and DLCO testing have been carried out annually since 1992.

People with at least one DLCO measurement constituted our study population. Participants were followed from the time of the first DLCO test available until the last DLCO test done before 23 September 2002. We excluded people under 25 years of age at baseline, as diffusing capacity is thought to peak at around that age.[5,13]

Determination of gas diffusion

DLCO was measured by the single-breath method, following the American Thoracic Society guidelines[14] and adjusting for standard haemoglobin concentration.[15] Measurements were considered adequate if inspiration reached at least 90% of forced vital capacity within 2 seconds and the subject's breath was held for 10 seconds. Testing was continued until two measurements were obtained within 10% of each other, or to a maximum of four tests, with a 10-minute interval between tests. The mean

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1 Demographic and exposure characteristics of the study population at the first measurement of DLCO

	Women	Men
Number of participants (%)	116 (12.4)	818 (87.6)
Mean DLCO (SD) (mL/min per mmHg*)	20.1 (4.5)	24.3 (6.7)
Number (%) of participants who were workers	52 (44.8)	724 (88.5)
Mean age (SD) (years)	54 (11)	58 (8)
Mean height at entry (SD) (cm)	161 (6)	172 (6)
Cumulative asbestos exposure (SD) (f/mL year†)	5.7 (8.3)	24.5 (45.7)
Mean number of years exposed to asbestos (SD)‡	2.4 (3.1)	1.3 (2.0)
Number of participants with radiographic asbestosis at baseline (%)	3 (2.6)	166 (20.3)
Mean number of years since last asbestos exposure (SD)	33.0 (6.7)	32.7 (5.6)
Mean age at first asbestos exposure (SD) (years)	18.0 (11.3)	24.2 (7.5)
Number of current smokers (%)	19 (16.5)	176 (21.5)
Number ex-smokers (%)	29 (25.2)	457 (56.0)
Number of never-smokers (%)	67 (58.2)	183 (22.4)

DLCO = carbon monoxide diffusing capacity. * Quantity of carbon monoxide absorbed per minute per mmHg pressure gradient from alveoli to pulmonary capillaries. † Number of fibres found in each millilitre of air multiplied by the number of years of exposure. ‡ Median 0.54 y (interquartile range, 0.20–1.63 y) for men; median 1.24 y (interquartile range, 0.58–3.00 y) for women. ◆

of the two technically acceptable determinations was used for our analysis. The unit for DLCO measurements is mL/min per mmHg (see Box 1 footnote).

DLCO measurements were performed at the Perth Chest Clinic and the Department of Pulmonary Physiology at Sir Charles Gairdner Hospital, using a Hewlett Packard Gas Transfer Analyser (Hewlett Packard, Palo Alto, Calif) or a Medical Graphics 1070 system (Medical Graphics, St Paul, Minn). The analysers were calibrated daily, their reliability was checked monthly, and maintenance was provided regularly. No important differences in results were observed between the two analysers.

Assessment of asbestos exposure

A quantitative estimate of cumulative asbestos exposure was made for each worker, using employment records and estimates of exposure based on historical records of measurements of crocidolite levels in the air of the workplace.[8,11,16] Cumulative exposure is expressed in "fibre/mL years", defined as the number of fibres found in each millilitre of air multiplied by the number of years of exposure (eg, 1 year worked at a level of 5 f/mL gives a cumulative exposure of 5 f/mL years).

Estimates of asbestos exposure for ex-residents were based on the few measurements of asbestos fibre levels made in the town, and consequently are more uncertain than those for the workers.[11,17] The estimates varied from 1 f/mL from 1943 to 1957 to 0.5 f/mL up to 1966, and finally decreased to 0.01 f/mL in 1992.

The calculations for both workers and residents were validated by comparisons with fibre counts in lung specimens and by the association between the exposure estimates and asbestos-related diseases.[8,16,17]

Radiographic assessment for asbestosis

A chest x-ray done at the first visit was used to determine whether asbestosis was present. X-rays were read by up to three trained readers following the International Labour Organisation classification.[18] Asbestosis was considered present if the x-ray was judged to have a parenchymal profusion score of 1/0 or greater,[11] based on the median reading of three observers. If the x-ray was read by only two readers, and they disagreed, the lower reading was accepted.[11]

Smoking history

Smoking history was self-reported at entry to the program. Participants who had smoked at least one cigarette per day for more than a month leading up to the first visit were classified as smokers, while those who had not smoked for at least 3 months before the visit were classified as ex-smokers.

Statistical analysis

After a basic description had been recorded and univariate analysis had been done to identify general trends, the dependent variable (DLCO) was regressed on time, asbestos exposure and smoking history, controlling for potential confounders such as sex, age and height. These data were analysed using a random-effects model, which allows participants to have an unequal number of observations and at different times.[19] All the explanatory variables were entered initially into the model, as well as the interactions between smoking and asbestos exposure.[11] The random effect was selected according to the likelihood ratio test, while the residual covariance structure was selected according to the Akaike information criterion.[19,20] Hypotheses for main effects were tested at the $\alpha = 0.05$ significance level, and those for interactions at the $\alpha = 0.01$ level. All analyses were conducted using SAS software version 8.2 (SAS Institute, Cary, NC, USA).

Ethics approval

All participants gave their informed consent and the study was approved by the Human Research Ethics Committee of the University of Western Australia and the Clinical Drug Trials Committee of the Sir Charles Gairdner Hospital, Perth.

RESULTS

There were 2980 measurements from 934 people who had at least one DLCO test. Apart from 146 participants who died during the observation period,[19] 279 (29.8% of all participants) dropped out of the study, without providing specific reasons. People who withdrew from the study had higher average levels of DLCO and tended to have had less exposure to asbestos.

Compared with women, men were exposed to higher cumulative amounts of asbestos (median, 6.6 f/mL per year; interquartile range, 2.1 f/mL–26.2 f/mL). A higher proportion of men had radiographic asbestosis, and a higher proportion of men were smokers or ex-smokers (Box 1).

During the observation period, participants had a varying number of DLCO determinations (median, 2; range, 1–17). As the vitamin A supplementation program initially enrolled people at higher risk of

2 Characteristics of the follow-up of the study population

	Women	Men
Number of participants (%)	116 (12.4)	818 (87.6)
Total number of measurements (%)	227 (7.6)	2753 (92.3)
Mean number of visits per person (SD)	2.1 (1.1)	3.5 (2.3)
Mean duration of follow-up in years (SD)	2.5 (2.7)	3.9 (3.2)
Mean number of months between measurements (SD)	28.4 (22.3)	18.5 (17.0)

3 Predictors of gas diffusion according to the random-effects model

Predictors	Effect on DLCO*	SE	*P*
DLCO at baseline (mL/min per mmHg)†	24.8	0.8	< 0.0001
Age at entry	–0.35	0.03	< 0.0001
Height at entry	0.22	0.02	< 0.0001
Female	–4.5	0.6	< 0.0001
Cumulative asbestos exposure	–0.006	0.003	0.11
Radiographic asbestosis at baseline	–3.0	0.4	< 0.0001
Age at first exposure	0.07	0.03	0.02
Current smoker	–5.1	0.4	< 0.0001
Ex-smoker	–1.4	0.3	0.0002
Years of follow-up‡	–0.33	0.02	< 0.0001
Interaction follow-up and radiographic asbestosis§	–0.22	0.05	< 0.0001

DLCO = carbon monoxide diffusing capacity. * Estimate of the fall in DLCO attributed to the predictor variable. † A DLCO value of 24.8 units corresponded, in our random-effects model, to a never-smoking man, 165 cm in height, aged 56 at study entry, first exposed to asbestos at age 20, with a cumulative asbestos exposure of 20 f/mL year and no baseline radiographic asbestosis. ‡ Represents the change in DLCO over time. § Represents the annual difference in DLCO change between people with radiographic asbestosis and those without radiographic asbestosis. ◆

developing asbestos-related diseases, the follow-up for workers (mostly men) was more comprehensive than that for ex-residents (mostly women) (Box 2).

According to the mixed model, the estimated DLCO level at baseline was 24.8 units (Box 3). Women had lower DLCO levels than men (4.5 units); age was inversely associated with DLCO levels (0.35 units lower, on average, for each additional year of age) (Box 3).

The average rate of decline of DLCO over the follow-up period was 0.33 (95% CI, 0.31–0.35) units per year, plus an additional decrement of 0.22 (95% CI, 0.12–0.32) units per year if the participant had radiographic asbestosis at the beginning of the follow-up period (Box 3).

The random-effects model (Box 3) also demonstrated that the presence of radiographic asbestosis at baseline was significantly associated with lower baseline DLCO levels — 3.0 (95% CI, 2.2–3.8) units lower on average than people without asbestosis. Further, people exposed to asbestos at a younger age had significantly lower DLCO levels at baseline. However, number of years since last exposure, exposure category (worker or resident) and cumulative asbestos exposure were not significant predictors of change in DLCO over time. (DLCO fell non-significantly, by 0.006 units for each additional f/mL year of exposure at baseline.)

Compared with never-smokers, DLCO in current smokers was 5.1 (95% CI, 4.7–5.5) units lower, and DLCO in ex-smokers was 1.4 (95% CI, 1.1–1.7) units lower. Smoking status did not affect the change in DLCO over the follow-up period. There was no significant interactive effect of smoking and asbestos exposure on either the level of DLCO or its change over time.

DISCUSSION

Our study is the first to report that asbestos exposure (measured as radiographic asbestosis) is significantly associated with accelerated decline in DLCO. In our study population (unique in being exposed exclusively to crocidolite), the gas diffusion capacity fell by an average of 0.33 units of DLCO per year. This is within the range of that found in other studies (0.19–1.02 units decrement in DLCO per year).[21-23] The average rate of decline of DLCO in people without asbestosis was about 1.3% per year (0.33/24.8), compared with about 2.2% per year (0.55/24.8) in people with asbestosis, a rate similar to the rate of decline in a small series of patients with chronic obstructive pulmonary disease (2.7% per year)[24] and a small series of asbestos-exposed workers (2.5% per year).[4]

We also found that lower gas diffusing capacity of the lung was associated with radiographic asbestosis, especially in people exposed at a younger age. Furthermore, although smoking was associated with lower DLCO levels, it did not affect the level or the rate of change of gas diffusion in this population, although this has been suggested for spirometric measures.[25] Our results suggest that the effects of tobacco smoking on the level or rate of change of gas diffusion are independent of those of asbestos exposure.

Other studies in different populations have also found that smoking is a significant predictor of DLCO at the beginning of follow-up.[4,21-23] However, these studies differ as to whether smoking also affects rate of change in DLCO, with some finding, as we did, no effect[4,22,23] and others finding that smoking results in a more rapid decrement with time.[21] Whatever the biological mechanism underlying this latter observation, it suggests that the reduced DLCO associated with smoking is a stepwise phenomenon occurring before initial DLCO testing.

Sex, age and height at entry have been reported as significant predictors of DLCO level in previous reports.[6,7] Our results confirmed this finding with regard to initial DLCO level, and further showed that the amount of change in DLCO over time is the same for men and women, regardless of their age and height. Others have reported different effects of demographic variables on the change of DLCO over time. For example, Burgess et al[21] found steeper rates of decline in men, while Sherril et al[26] and Viegi et al[13] reported no difference between sexes, but accelerated decline in older people. The study of different occupational

settings and the use of different analytical techniques may explain these conflicting results.

A particular strength of our study was the use of a random-effects model, which models individual measurements for each participant. Thus, although data from participants with only one measurement are not included in estimating the rate of change, they do increase the precision of the estimation of DLCO.[19] Further, our longitudinal model included height, sex and age, accounting for the main sources of variability in alveolar volume.

However, a number of limitations should also be noted. The study sample may not be truly representative of the asbestos-exposed population at Wittenoom, as previous reports have shown that participants in the vitamin A program were younger and had higher asbestos exposures compared with non-participants.[11]

Furthermore, it was not feasible to meet the American Thoracic Society recommendation of stopping smoking for 24 hours before the test. This is likely to have affected DLCO measurements because of the presence of carboxyhaemoglobin,[7] which would tend to accentuate differences between current smokers and ex-smokers or never-smokers.

Lastly, while survival bias (duration of disease influencing exposure measurements) is not a concern in cohort studies, the fact that there were missing data (due to withdrawals) may result in follow-up bias in our study.[27]

Our study confirms the deleterious effect of crocidolite on DLCO and shows, for the first time, that this damage not only persists but also worsens over time. Our results also show that smoking and asbestos exposure affect the level and rate of decline of DLCO in an additive, rather than synergistic, manner in this population.

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COMPETING INTERESTS

None identified.

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