MESOTHELIOMA AFTER ENVIRONMENTAL CROCIDOLITE EXPOSURE

J. Hansen,* N. H. de Klerk,† A. W. Musk,* J. L. Eccleston† and M. S. T. Hobbs†

*Department of Respiratory Medicine, Sir Charles Gairdner Hospital; and †Department of Public Health, University of Western Australia, Nedlands, 6907 Western Australia, Australia

INTRODUCTION

It is well-known that occupational exposure to asbestos, especially crocidolite, causes mesothelioma (Dement et al., 1994; McDonald et al., 1993; Newhouse and Sullivan, 1989; Armstrong et al., 1988) and that the rate of mesothelioma increases with both level of exposure and time since first exposure (de Klerk et al., 1989; Peto, 1985). That non-occupational, or environmental, exposure to asbestos results in an increased risk of mesothelioma is no longer in doubt (Magnani et al., 1993; Joubert et al., 1991; Reid et al., 1990; Wagner et al., 1960). It appears that exposure to crocidolite, particularly by living in the vicinity of a mine or mill, confers the greatest risk (Reid et al., 1990; Siemiatycki, 1982). No previous study of environmental exposure to asbestos and risk of mesothelioma has been able to assess exposure levels which would make the derivation of exposure–response relationships possible (Dodoli et al., 1992; Reid et al., 1990; Siemiatycki, 1982; Hammond et al., 1979).

Nearly 7000 people were employed by the Australian Blue Asbestos (ABA) Company at the Wittenoom crocidolite mine and mill between 1943 and 1966. They experienced an increased risk of mesothelioma which was dose-dependent (Armstrong et al., 1988). A cohort of former residents of Wittenoom, who lived there for at least one month between 1943 and 1993 and were not directly employed in the mining and milling of crocidolite, has been established (Hansen et al., 1993). These residents include: the wives and families of former ABA employees; government employees, such as teachers, hospital staff and police; people who worked for other mining companies which used Wittenoom as a base camp for exploration of the surrounding area; people who were self-employed; and families of these people.

Information was obtained from numerous sources, including the local school register, hospital attendances, the WA electoral roll, birth certificates, information provided by Wittenoom crocidolite workers who answered a mailed questionnaire in 1979 and participants in a cancer-prevention programme using vitamin A dietary supplements. This study aims to estimate exposure–response relationships between mesothelioma and environmental exposure to crocidolite in these subjects.
METHODS

All subjects who claimed to have worked with crocidolite at Wittenoom, were excluded from the cohort. Before proceeding with death and disease searches, all females not traced to a current address were sought in the WA marriage register, commencing the year she was last known to be alive, or, for those not known to have married, the year she turned 15. Computerised record linkage procedures were used to search the annual death index for WA from 1969 to 1993, to determine the numbers and causes of deaths to arise in this cohort. Prior deaths were found by manually searching of records from 1943 to 1968. The coded cause of death was routinely extracted from the death tapes for deaths since 1969, or coded by an experienced nosologist for other deaths. Records of all cases of malignant mesothelioma in WA are registered by the WA Mesothelioma Registry. The Australian Mesothelioma Surveillance Programme is notified of other cases occurring elsewhere in Australia. Records of both these registries were inspected to obtain cases arising in this cohort.

The current address of people who were not known to have died and who were not participating in the vitamin A cancer prevention programme, was obtained from the WA Electoral Roll, the Commonwealth Electoral Roll or through relatives. They were mailed a questionnaire which gathered information on the time they spent at Wittenoom, smoking and medical histories and demographic data. Participants of the vitamin A programme provided this information when they enrolled in the programme.

The level of individual exposure was estimated for each subject in the cohort (Hansen et al., 1996). Briefly, subjects not working for ABA directly with crocidolite at Wittenoom were estimated to have an intensity of exposure of 1.0 \( \text{fml}^{-1} \) from 1943 to 1957 (when a new mill was commissioned and the town was moved from being adjacent to the mill to a site 10 km away) and then 0.5 \( \text{fml}^{-1} \) between 1958 and 1966, when the mining operations ceased. Since then, exposure of residents in the town continued because of the widespread use of tailings around the town, and individual exposures were assigned by interpolation from periodic surveys from 0.5 \( \text{fml}^{-1} \) in 1966 to 0.014 \( \text{fml}^{-1} \) in 1992. Duration of residence was combined with intensity of exposure to give a measure of cumulative exposure for each person, which was adjusted to account for the continuous nature of exposure experienced by these subjects.

Mesothelioma incidence rates were standardised to the World Population. Cox regression (Cox, 1972) was used to examine the separate and combined effect of age, sex, time since first residence at Wittenoom, estimated levels of exposure and age at first exposure on the incidence of mesothelioma. Length of stay at Wittenoom and cumulative exposure were treated as time-dependent covariates, and age at first exposure, sex, calendar period of first exposure, whether a subject lived with an asbestos worker, or washed the clothes of an asbestos worker, were included as fixed covariates. Data were censored at 31 December, 1993 or age 85, whichever occurred first and the “survival time” variable used was time since first residence at Wittenoom. The best transformation for each variable, where appropriate, (categorical, log or untransformed) was assessed by linearity of trends and likelihood ratio criteria and included in the final model if they improved the fit \((P < 0.05)\).
RESULTS

One hundred and fifty one subjects claimed to have worked with crocidolite at Wittenoom and were excluded from the cohort. To the end of 1993, 27 cases of malignant pleural mesothelioma had been diagnosed and histologically confirmed by either the WA Mesothelioma Registry or the Australian Mesothelioma Surveillance Programme. A further five cases arose in subjects excluded from this cohort who worked with asbestos at Wittenoom. Another 17 cases of mesothelioma were reported to the WA Mesothelioma Registry who claimed to have had exposure to crocidolite at Wittenoom. They have not been included in this study because their residence was short and was not independently established by methods previously described (Hansen et al., 1993).

Of the 18 female and 9 male cases, 25 arose in people who also experienced "domestic" exposure as they had lived with men who worked with crocidolite at Wittenoom. So far, only 1 case has arisen in a resident who first went to Wittenoom after the mining operations ceased in 1966. Sixteen of the cases (59%) had occurred since 1989. No cases arose within 20 years of first residence at Wittenoom.

When compared with the rest of the cohort, mesothelioma cases stayed longer at Wittenoom (mean stay 65 months vs. 33 months, \( P < 0.001 \)), had a higher average intensity of exposure (mean value 0.3 \( \text{fml}^{-1} \) vs. 0.5 \( \text{fml}^{-1} \), \( P < 0.001 \)), and a higher cumulative exposure to crocidolite (16.3 \( \text{fml}^{-1} \) vs 5.4 \( \text{fml}^{-1} \), \( P < 0.001 \)). The standardised incidence of mesothelioma to 1993 in this cohort was 207 per million person-years (pmpy) and was similar for males and females (186 and 210 pmpy, respectively). The rate increased significantly with time from first exposure, duration of exposure and cumulative exposure. Incidence rose from 180 pmpy 20-29 years since first exposure, to 791 pmpy 30-39 years since first exposure and 999, 40 or more years since first exposure. Over all times from first exposure, the incidence of mesothelioma rose from 57 pmpy for those who lived at Wittenoom for less than 1 year, to 143 pmpy for residents with duration of residence between 1 and 5 years, to 720 pmpy for those who lived at Wittenoom longer than 5 years. The incidence of mesothelioma was 87 pmpy for subjects whose estimated cumulative exposure was less than 7 \( \text{fml}^{-1} \), rising to 327 and 1544 pmpy for estimated cumulative exposure of 7-20 \( \text{fml}^{-1} \) and over 20 \( \text{fml}^{-1} \), respectively.

In all regression models, age at first exposure, sex, year of first exposure, intensity of exposure, whether a subject lived with an asbestos worker or washed his clothes, had no significant effect on mesothelioma incidence (\( P > 0.05 \)). Relative risks of mesothelioma were significantly increased to 2.5 (exposure duration: 1–5 years) and 6.2 (exposure duration > 5 years), compared to subjects who stayed at Wittenoom for less than 1 year (\( P < 0.001 \)); and to 2.5 (cumulative exposure: 7–20 \( \text{fml}^{-1} \)) and 6.3 (cumulative exposure > 20 \( \text{fml}^{-1} \)), when compared to subjects whose cumulative exposure was less than 7 \( \text{fml}^{-1} \) (\( P < 0.001 \)).

DISCUSSION

This study of former residents of Wittenoom who were environmentally exposed to crocidolite shows that the incidence of mesothelioma increased significantly with
increasing time from first residence at Wittenoom and with increasing level of exposure, whether assessed by duration of residence or by cumulative exposure. The incidence of mesothelioma increased from about 180 per million person-years (pmpy) at 20–29 years since first exposure, to 1000 pmpy at 40 or more years from first exposure. No figures are available from studies of other environmentally exposed subjects, but the corresponding figures for the Wittenoom workers’ cohort were approximately 900 and 7000 pmpy and typically about 1000 pmpy and 5000 pmpy for other occupational cohorts (de Klerk and Armstrong, 1992).

Regression analysis also showed evidence of an exposure–response relationship with mesothelioma incidence in this cohort. When duration of residence and estimated intensity of exposure were included in the model together, the association between rate of mesothelioma and intensity of exposure was not significant. This result was not unexpected as intensity of exposure was measured with much more error than duration of residence (Hansen et al., 1996), and the amount of error introduced into the estimate of cumulative exposure by the estimate of intensity of exposure could explain why the model using just duration of residence appeared a better fit than the one using cumulative exposure.

This is the first study to show exposure–response relationships between incidence of mesothelioma and environmental exposure to any form of asbestos. The study of a birth cohort of exposed subjects near South African crocidolite mines has been unable to determine the intensity and duration of exposure for members of the cohort (Reid et al., 1990).

Wittenoom residents in this study experienced a standardised incidence rate of mesothelioma of around 210 pmpy, which is substantially higher than the Western Australian rate in 1988 of 50 pmpy for men and 8 pmpy for women (de Klerk and Armstrong, 1992). It is exceeded in Australia only by that found among Aboriginal residents of the Pilbara region of WA, who have a crude rate of 250 pmpy (Musk et al., 1995), and is one of the highest population rates in the world (de Klerk and Armstrong, 1992). Other studies of environmental asbestos exposure have reported high rates among specific populations, including residents near an asbestos-cement factory in Italy who experienced age-standardised incidence rates of 114 pmpy for males and 73 pmpy for females (Magnani et al., 1993).

Most population studies of mesothelioma report differences in the incidence rates for men and women with the rates for males being typically 5–9 times greater than those for females. This is thought to be due to a much greater proportion of male cases having prior occupational exposure to asbestos than females (Leigh et al., 1991). Females are more likely to obtain their exposure environmentally. Similar mesothelioma incidence rates for males and females shown in this study reflect the nature of exposure: both males and females were exposed to crocidolite by living in Wittenoom and men with known occupational exposure to crocidolite at Wittenoom were excluded from the analysis.

In conclusion, this study has shown that at the “low” levels of crocidolite exposure experienced by former residents of Wittenoom, there is a significantly increased risk of mesothelioma, which is dose-dependent.
REFERENCES


