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# Case-Control Study of Mesothelioma in South Africa

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**Background** *South Africa has, uniquely, mined, transported, and used crocidolite, amosite, and chrysotile. A multicenter case-control study was done in South Africa to examine the details of asbestos exposure in cases and controls, and to calculate relative risks for level of certainty of asbestos exposure, nature of exposure (e.g., environmental, occupational) and fiber type.*

**Methods** *Cases and controls (one cancer and one medical per case) were collected by six study centers from referral hospitals, and exposure information was collected by interviewing cases and controls in life.*

**Results** *One hundred and twenty-three cases were accepted into the study. None had purely chrysotile exposure. Twenty-three cases had mined Cape crocidolite; three had mined amosite; and three Transvaal crocidolite plus amosite. A minimum of 22 of the cases had exclusively environmental exposure, 20 were from the NW Cape crocidolite mining area. The relative risks associated with environmental exposure in the NW Cape (crocidolite) were larger than for environmental exposure in the NE Transvaal (amosite and crocidolite): 21.9 vs. 7.1 and 50.9 vs. 12.0 for the cancer control and medical control datasets, respectively.*

**Conclusions** *The results confirm the importance of environmental exposure in the Cape crocidolite mining area, the relative paucity of cases linked to amosite, the rarity of chrysotile cases and are consistent with a fiber gradient in mesotheliomagenic potential for South African asbestos with crocidolite > amosite > chrysotile.* Am. J. Ind. Med. 35:213–222, 1999. *© 1999 Wiley-Liss, Inc.*

***KEY WORDS: mesothelioma; South Africa; case-control; asbestos; chrysotile; amosite; crocidolite***

## INTRODUCTION

South Africa has, uniquely, mined, transported and used crocidolite, amosite, and chrysotile, the three main commercial varieties of asbestos. It is, thus, no surprise that mesothelioma rates are relatively high [Zwi et al., 1989]. Somewhat surprising, though, is the paucity of local epidemiologic studies of this disease — many questions about mesothelioma in South Africa remain unanswered, among them the relative contribution each variety of asbestos makes to the case load; the extent and nature of asbestos exposure in a representative group of cases (for instance, the proportion of cases with purely environmental exposure);

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and the relative risks associated with the different fiber types and exposure settings.

These questions are of more than local interest. The amphibole hypothesis, which has it that amphiboles are the only asbestos which cause mesothelioma, is topical and controversial [Stayner et al., 1996; Smith and Wright, 1996], and South African asbestos has been exported to many countries.

The data reported here are from a South African multicenter case-control study. The major objectives of the study were to examine asbestos exposure in detail in South African cases and to calculate relative risks for level of certainty of asbestos exposure (i.e., definite, probable, possible, and unlikely), for category of exposure (e.g., occupational and environmental) and for fiber type. Nonasbestos agents and mesothelioma and the possible protective effect of consumption of vegetables on the development of mesothelioma were also studied; these results are reported elsewhere.

## MATERIALS AND METHODS

This multicenter case-control study of mesothelioma used a secondary base of referral hospitals for cases and controls and collected exposure information prospectively: cases and controls were interviewed in-life by trained interviewers using a standard questionnaire.

### Study Centers and Research Teams

The study was conducted in the six major industrial centers of South Africa, and each center included all hospitals within 50 km of the city center. Greater Bloemfontein, Cape Town, Durban, Johannesburg, Kimberley, Port Elizabeth, and Pretoria were selected as study centers because they are the major industrial cities and are geographically located so that their tertiary hospitals serve much of South Africa, including the asbestos mining regions (without being in an asbestos mining district itself). Durban was later abandoned as a study center as it did not operate successfully. A research team comprising a coordinator and two interviewers, between them fluent in English and the predominant vernaculars, was established in each study center. Each team was trained using a detailed interactive instruction manual as pre-reading followed by a day-long training session. Interviewers were blind to case-control status of subjects and did not know that the primary research questions concerned asbestos and mesothelioma. Research teams operated for about 16 months, from late 1988 through early 1990. (The relatively short duration for case collection was to prevent declining motivation of researchers likely to occur over an extended study period.) Motivation was maintained through regular contact, a newsletter, and practice interviews when long periods between cases occurred.

### Cases

Our intention was to include all cases treated or diagnosed in the study centers over the study period. To achieve this, all pathologists, oncologists, cardiothoracic surgeons, and respiratory physicians registered in the study centers were invited by mail and telephone to refer new cases to the research teams. In addition, to encourage participation, key practitioners most likely to encounter cases (for instance, heads of units in large hospitals or practitioners with a known interest in the condition) were visited by research teams. All of these medical practitioners were reminded regularly of the study and were sent brightly colored reminder cards at intervals for display in their rooms.

To reduce diagnostic misclassification (increase the true positive rate), cases were entered into the study only if a specialist pathologist diagnosed mesothelioma, the histologic diagnosis was supported on review by a member of the South African Asbestos Tumour Reference Panel (a panel of experienced specialist pathologists established to standardize the histologic diagnosis of mesothelioma), and immunohistochemical staining supported the diagnosis with a minimum requirement of negative staining for carcinoembrionic antigen (CEA).

### Controls

Two controls, one with a medical condition and the other with cancer, were selected for each case. Cases and controls were matched on the hospital in which the case was interviewed, skin color, gender, and approximate age (within 5 years). General exclusion criteria for both medical and cancer controls were that they should not have asbestos-related disease or an undiagnosed condition (i.e., diagnostic investigation incomplete). Controls with lung, pleural, or peritoneal malignancy were excluded, as were patients disoriented for time, place, or person and individuals with conditions of the central nervous system (to avoid selection of controls with disease-related memory deficits). To increase the likelihood that cases and controls were from the same population base with the same referral dynamics and pressures into the source hospital, controls were limited to patients with a serious condition likely to warrant similar medical referral pressures as patients with the signs and symptoms of mesothelioma. Referral hospitals often serve the primary medical care and secondary level needs of the local community as well as providing tertiary level services. To avoid misrepresentation through selection of these patients with relatively minor conditions (unlike mesothelioma cases), skin cancer patients were excluded as were all medical patients with fewer than five in-patient days (for the current admission).

## Exposure Information

Exposure information was obtained directly from cases and controls by (1) the administration of a structured questionnaire after obtaining written informed consent; and (2) the examination of sputum samples for coated fibers.

### *The questionnaire*

A detailed questionnaire on residential and occupational history and domestic exposures was administered in the preferred language of the subject in a standard manner by the interviewers. To reduce interviewer bias, questions were largely closed-ended or tightly structured, thus allowing little interpretation by the interviewer even if case/control status was inadvertently known. Some open-ended questions were asked toward the end of the interview to promote completeness of information. The questionnaire included a residential history (town and magisterial district), time spent near dockyards, mines, mills, asbestos using factories, stores of asbestos, parents' occupation, domestic and leisure time exposure to dust, a complete occupational history with detailed questioning on asbestos exposure, and questions on diet and tobacco smoking. Two components of the questionnaire were developed as ''memory joggers'' to aid recall of particularly important potential sources of asbestos exposure. One section enumerated districts in which asbestos had been mined and the other listed important industries, occupations, and activities with a known risk of asbestos exposure. The industry and occupation lists were compiled by collating information from three sources: literature, consultation with experienced occupational health practitioners, and the patient database of the Occupational Medicine Clinic of the National Centre for Occupational Health (NCOH). General references [Health and Safety Commission, 1979a,b; Michaels and Chissick, 1979; Parmeggiani, 1983; Nicholson et al., 1982] were consulted to compile an initial list. To this was added the important exposure settings reported by patients who had attended the clinic — patients were cross-filed by exposure category and these were used. The list was then refined by two experienced occupational medicine practitioners and two experienced occupational hygienists who together produced the final 31 primary memory joggers or occupational risk settings (Appendix).

Nondifferential recall bias favoring greater recall by cases is theoretically possible if cases have been questioned repeatedly prior to the study interview, or if an advantage (e.g., compensation) is conferred through a positive history. To reduce this bias, cases were interviewed as soon as the diagnosis was suspected (82% of cases had their first exposure history taken by an interviewer for this study) and subjects were not told that the study related to asbestos specifically, but rather explored a variety of diseases and exposures, thus placing cases and controls in the same position regarding possible work-relatedness and compensation.

### *Coated fibers in sputum*

The validity of exposure data derived from questionnaires is affected by failure to recall or recognize past exposure. In an attempt to identify some of the ''failures'' in this study, spontaneous sputum samples (i.e., sputum samples not induced by inhalation of aerosol) were collected from subjects for evaluation of coated fibers. (The term coated fibers is used synonymously with ferruginous bodies.) An attempt was made to collect two sputum samples from each study subject, the first after completion of the questionnaire and, in an attempt to collect a 24-hr sample, a container was left with the subject for post-collection in a prepaid envelope. Sputum examination was done at the NCOH by experienced technicians blind to case-control status using a standard technique [Smith and Naylor, 1972].

## Asbestos Exposure Categories

Subjects were grouped by probability of exposure to asbestos (exposure class), the likely fiber type, and the nature of this exposure (e.g., occupational or environmental).

### *Exposure classes*

Table I shows the criteria for allocation of subjects to one of definite, probable, possible, or unlikely asbestos exposure class.

The magisterial districts of South Africa were divided into five groups: NW Cape (Cape crocidolite mining); NE Transvaal (amosite and/or Transvaal crocidolite mining); E Transvaal (chrysotile mining); ''Other'' districts (minor asbestos deposits — anthophillite, chrysotile, or tremolite mined in a small locality for a short period in some districts); and nonasbestos districts (no asbestos deposits). The period spent in any of the asbestos districts was recorded for each subject using the questionnaire data. (Note: the boundaries and names of South Africa's provinces have changed but the old names have been retained in this article for concordance with previous literature. NW Cape is now Northern Cape Province and North West Province, NE Transvaal is the Northern Province, and E Transvaal is Mpumalanga.)

Living ''near'' an asbestos mine or mill was not restricted to a specified distance, since it is well known that extensive areas around mines and mills were contaminated, particularly in the NW Cape [Marchand, 1991] and NE Transvaal [Felix et al., 1994]. ''High risk'' occupations or activities are those listed in the Appendix in which asbestos exposure was thought to be probable even if the subject did not actually recall exposure: 1 A, C, F, L, M, P, R, S, U, and

**TABLE I.** Criteria for Allocating Cases and Controls to Asbestos Exposure Classes

Definite

1. Direct or indirect occupational exposure reported.
2. Contact with asbestos while spending time in an asbestos mining district (contact included playing on tailings dumps; living near a mine or mill; parent working in a mine or mill; asbestos fiber contaminating work or domestic environment).
3. Domestic exposure reported.

Probable

1. Worked in ''High risk'' occupational or activity without recall of occupational exposure.
2. Spent 12 months or longer in an asbestos mining district of NW Cape, NE Transvaal, or E Transvaal without reported contact with asbestos.
3. Co-resident worked with asbestos products in the residence.

Possible

1. Worked in a ''Risk'' occupation without recall of occupational exposure.
2. Spent less than 12 months in NW Cape, NE Transvaal, or E Transvaal district without recall of contact.
3. Domestic use of asbestos cement products or heating panels.
4. Lived or worked in an asbestos cement structure.
5. Lived or worked within 1 km of a dockyard or asbestos product manufacturing factory.
6. Uncertain direct or indirect occupational exposure reported.

Unlikely

No recall of exposure.

No ''Risk'' or ''High risk'' occupation or activities.

Lived in ''Other'' district without reported contact.

V were labeled ''High risk'' while the rest of 1 (excluding sugar-cane) and 2 were labeled ''Risk'' occupations or activities.

Other districts mined asbestos in limited quantities in a small section of the district, often for only a relatively short period. Consequently, asbestos exposure was considered unlikely merely as a result of residence in other districts — reported contact with asbestos, however, led to a classification of ''Definitely exposed.''

### *Fiber type*

Whether asbestos exposure had occurred exclusively to a single fiber type could not be determined confidently in many subjects. For example, asbestos cement product users (chrysotile plus amphibole or only chrysotile in more recent times), and those with possible exposure in a risk occupation or residence in a number of NE Transvaal mining districts (amosite and/or Transvaal crocidolite). For this reason, fiber-specific odds ratio calculations were limited to three situations:

1. District-specific risks — subjects with asbestos exposure exclusively in the NW Cape (Cape crocidolite); NE Transvaal (amosite and/or Transvaal crocidolite), or E Transvaal (chrysotile) were used for these analyses.
2. Those in whom crocidolite exposure had occurred even if this was not necessarily limited to crocidolite. Subjects in this category were those who had spent time in the NW Cape (residence, mining crocidolite, transporting crocidolite, etc.), who reported exposure in the manufacture of battery casings or large diameter water pipes and those who reported crocidolite exposure (for example, blue asbestos mining or milling).
3. Workers with exposure exclusively in asbestos mining or mining-related work.

### *Nature*

Nature of exposure was categorized as occupational, environmental, domestic, or incidental. Direct occupational was use at work by the subject while ''Indirect'' was exposure due to the use of asbestos by coworkers; ''High risk'' and ''Risk'' activities are shown in the Appendix. ''Environmental-mining'' was exposure due to contamination of the general environment by asbestos mining, milling, and related activities, while ''Environmental-other'' exposure arose from living within a kilometer of an asbestos-using factory, store of asbestos, or dockyard. Domestic exposure occurred at home due either to contaminated workclothes (Domestic-clothes) or work with asbestos products (Domestic-use), which included hobbies and the servicing of motor vehicles' brakes. Incidental exposure was use of asbestos cement garden furniture, spending time in asbestos cement structures, and use of asbestos heating panels.

## Data Management and Analysis

All data were coded blind to the case-control status of the subject by the principal researcher, and subsequent allocation to exposure classes, fiber types, and nature of exposure was done without knowledge of diagnosis or sputum results. Questionnaires were double-punched and the datasets were compared and corrected by referring to the original questionnaire.

Univariate and bivariate statistical analysis was done with the assistance of the Epiinfo Version5 software program [Dean et al., 1990]. Conditional logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI) using the EGRET Software Package [Egret, 1991]. The cases and cancer controls and cases and medical controls were treated as two separate datasets, unless otherwise stated, and matching was retained in analysis. In some analyses, medical and cancer controls were pooled with a view to examining the effect of greater power on the effect estimates and their confidence intervals, on the assumption that the two sets of controls did not represent different populations. In these pooled analyses, matching was also retained to produce triplets of one case and two controls and conditional logistic regression was used to calculate ORs. Odds ratios and 95% CI were calculated for class and nature of asbestos exposure and occupation-specific ratios were calculated for Cape crocidolite miners and for workers who had had contact with asbestos insulation material and for workers using asbestos cement.

## RESULTS

One hundred and twenty-three cases were accepted into the study; tumor site, sex, and mean age are shown by study center in Table II. One hundred and nineteen cancer controls and 103 medical controls were available for analysis. Since there were 123 cases, the datasets were four cancer and 20 medical controls short. This arose in the cancer control dataset because of inappropriate controls being selected (e.g., not matched by age, hospital, or skin color, or disease not a cancer) and in 19 medical controls because medical controls were not interviewed in the Bloemfontein region and this could not be rectified before the study team was disrupted. The remaining medical control had a pleural effusion and was therefore excluded as mesothelioma was possible.

Table III shows the subjects by exposure class. There was no significant difference in exposure class between the two sets of controls.

The nature of asbestos exposure (as explained above) is shown for cases and controls in Table IV. Only three cases were categorized ‘‘None’’ — these three plus the two cases categorized ‘‘Other’’ district only make up the ‘‘Unlikely’’ class of Table III. The two control groups were very similar in their distribution of nature of exposure. Twenty-two cases (17.9%) had exclusively environmental exposure in one of the three main asbestos mining regions; 20 in the NW Cape, one in the NE Transvaal, and one in both the E Transvaal (369 months) and the NE Transvaal (3 months). Two cases had ‘‘Domestic-use’’ as the major source of exposure: one built his own house and cut asbestos ceilings and the other was exposed while her husband insulated their house. An inspection of the house revealed asbestos lagging on water pipes between the roof and ceiling. The lagging material was examined by X-ray diffractometry and found to be 0.5–1% chrysotile and 0.5–2% either amosite or crocidolite (personal communication, RSJ du Toit, NCOH, 1989). This woman had another possible source of exposure as she had worked as a pay clerk and visited construction sites for about 30 min per week for many years.

Table V presents cases and controls grouped into four major occupational exposure categories. Twenty-eight subjects had worked on Cape crocidolite mines. Two of these mines are unknown (Beeshoek and Roddies) — both were named by controls. It is notable that no subject had worked at a chrysotile mine.

**TABLE II.** Characteristics of Mesothelioma in Case-Control Study in South Africa 1988–1990

| | Site* | | Sex | | Age |
|---|---|---|---|---|---|
| | Pleura | Peritoneum | Male | Female | Mean (SD) |
| Johannesburg n = 48 | 44 | 3 | 43 | 5 | 55.8 (13) |
| Pretoria n = 21 | 20 | 1 | 15 | 6 | 58.2 (11) |
| Kimberley n = 22 | 20 | 2 | 16 | 6 | 52.6 (12) |
| Bloemfontein n = 19 | 18 | 1 | 16 | 3 | 52.3 (10) |
| Cape Town n = 10 | 10 | 0 | 9 | 1 | 58.9 (15) |
| Port Elizabeth n = 3 | 3 | 0 | 3 | 0 | 57.3 (7) |
| TOTAL (%) | 115 (94) | 7 (6) | 102 (83) | 21 (17) | 55.4 (12) |

*Excludes pericardium: Johannesburg = 1 case.

**TABLE III.** Mesothelioma Cases and Controls by Exposure Class,* South Africa 1988–1990

| | Cases | Cancer controls | Medical controls |
|---|---|---|---|
| Class | n (%) | n (%) | n (%) |
| Definite | 94 (75) | 24 (20) | 20 (19) |
| Probable | 14 (11) | 16 (13) | 15 (15) |
| Possible | 12 (10) | 39 (33) | 33 (32) |
| Unlikely | 5 (4) | 40 (34) | 35 (34) |
| Total | 123 | 119 | 103 |

*See Table I.

A proportion of the cases and the controls had had no asbestos exposure other than that which may have occurred due to living in or visiting an asbestos mining district or from occupational or other contact with the district-specific asbestos while spending time in the particular district. In these individuals, asbestos fiber type could be confidently identified, as the exposure had been exclusively in the mining district to the asbestos mined in the district. These individuals are presented in Table VI by case-control status. The subjects presented in Table VI include all those with occupational mining-related exposure shown in Table V (n = 35) plus 57 other subjects whose only asbestos exposure was district-specific while working, residing, or spending time in an identified mining district. No case reported E Transvaal exclusive exposure.

Table VII presents ORs and 95% CIs for cases matched with a cancer and a medical control (i.e., 1:2 matching) and for cancer and medical controls separately (1:1 matching). In the 1:2 matching, only 103 triplets were available for analysis since complete triplets could not be formed unless

**TABLE IV.** Nature of Asbestos Exposure in Mesothelioma Cases and Controls, South Africa, 1988–1990

| Nature | Cases n (%) | Women cases n (%) | Cancer controls n (%) | Medical controls n (%) |
|---|---|---|---|---|
| Occupational | | | | |
| Direct | 63 (51) | 1 (5) | 18 (15) | 14 (14) |
| Indirect | 9 (7) | 1 (5) | 3 (2.5) | 3 (3) |
| ''High risk'' | 0 | 0 | 1 (1) | 4 (4) |
| ''Risk'' | 8 (7) | 0 | 23 (19) | 19 (18) |
| Uncertain | 2 (2) | 0 | 1 (1) | 3 (3) |
| Environmental | | | | |
| Mining | 22 (18) | 15 (71) | 15 (13) | 12 (12) |
| Other | 0 | 0 | 3 (2.5) | 2 (2) |
| +Uncertain occupational | 4 (3) | 1 (5) | 0 | 2 (2) |
| +''Risk'' | 8 (6) | 0 | 12 (10) | 8 (8) |
| ''Other'' district only | 2 (2) | 1 (5) | 2 (2) | 1 (1) |
| Domestic | | | | |
| Clothes | 0 | | 0 | 0 |
| Use | 2 (2) | 1 (5) | 1 (1) | 0 |
| Incidental | 0 | | 2 (2) | 2 (2) |
| None | 3 (2) | 1 (5) | 38 (32) | 33 (32) |
| TOTAL | 123 | 21 | 119 | 103 |

**TABLE V.** Major Categories of Occupational Asbestos Exposure in South African Mesothelioma Cases

| | Mining and related work* | | | | | Asbestos cement | | |
|---|---|---|---|---|---|---|---|---|
| | CC | TC | A | TC + A | Cr | Building products | Pipes | Insulation work |
| Cases (n = 123) | 23 | 1 | 3 | 3 | 0 | 10 | 2 | 22 |
| Cancer controls (n = 119) | 2 | 0 | 0 | 0 | 0 | 9 | 0 | 4 |
| Medical controls (n = 103) | 3 | 0 | 0 | 0 | 0 | 5 | 0 | 6 |

CC = Cape crocidolite, TC = Transvaal crocidolite, A = Amosite, Cr = Chrysotile.
*TC mine = Transvaal Blue Asbestos; A mine = Penge; TC + A mines = Matshikane (Mafefe), Coco and Makapeng (Mafefe), Lucerne (Mafefe).
CC mines = Bretby, Cape Blue Asbestos, CBM, KCB, Koegas, Kuruman, Pomfret, Riries, Whitebank, Beeshoek, Roddies.

**TABLE VI.** Subjects With Asbestos Exposure Exclusively in South African Asbestos Mining Districts

| Region | Cases n (%) | Cancer controls n (%)* | Medical controls n (%)* |
|---|---|---|---|
| N W Cape | 44 (36) | 11 (9) | 7 (7) |
| N E Transvaal | 7 (6) | 4 (3) | 4 (4) |
| E Transvaal | 0 | 6 (5) | 2 (2) |
| ''Other'' | 2 (2) | 3 (3) | 2 (2) |

Number of cases = 123, cancer control = 119, medical controls = 103.
*Percent of all cases or controls.

**TABLE VII.** OR for Mesothelioma According to Class and Nature of Asbestos Exposure[a]

| Asbestos exposure | Cancer and medical[c] OR | Cancer and medical[c] 95% CI | Cancer controls OR | Cancer controls 95% CI | Medical controls OR | Medical controls 95% CI |
|---|---|---|---|---|---|---|
| Possible | 4.4 | 0.96–20.5 | 1.7 | 0.4–8.2 | 10.0 | 0.9–108.7 |
| Probable | 5.5 | 1.4–22.5 | 7.5 | 1.7–37 | 10.5 | 1.2–89 |
| Definite | 58.7 | 14.0–246 | 40.8 | 9.2–109 | 104.5 | 10.6–1026 |
| Nature[b] | | | | | | |
| Occupational | 80.6 | 15.7–414 | 45.9 | 8.0–262 | 38.9 | 9.7–182.8 |
| Environmental | 19.6 | 3.7–105 | 12.2 | 2.2–67.0 | 15.1 | 3.3–79.9 |
| ''Risk'' occupation | 15.9 | 2.9–84.3 | 3.3 | 0.5–20.2 | 2.3 | 0.4–13.9 |
| Occupational | | | | | | |
| Mining CC | 85.5 | 14.5–505 | 160.5 | 11–2339 | 145.4 | 11.2–1885 |
| Insulation | 76.4 | 14.4–406 | 163.3 | 11.2–2374 | 87.3 | 8.3–918 |
| Asbestos cement | 27.7 | 4.9–154 | 13.8 | 2.3–83 | 43.6 | 3.9–486 |
| Environmental[b] | | | | | | |
| NW Cape | 32.7 | 8.1–131 | 21.9 | 4.7–102.4 | 50.9 | 7.2–360 |
| NE Transvaal | 12.7 | 1.9–84.7 | 7.1 | 0.2–171 | 12.0 | 1.2–117 |
| Crocidolite | | | | | | |
| <2 months | 20.7 | 2.8–151 | 5.6 | 0.8–37.9 | 31.9 | 2.1–492 |
| any | 72.7 | 14.5–365 | 57.9 | 10.9–309 | 68.1 | 8.0–578 |

CC = Cape crocidolite.
[a]Base level of exposure = unlikely exposure class.
[b]Occupational = direct or indirect occupational exposure reported by subject; Environmental = time spent in a mining district the only source of exposure. Risk occupation = worked in a ''Risk'' occupation associated with exposure but no recall.
[c]1:2 Matching with case and a medical plus a cancer control.

both a medical control (n = 103) and a cancer control (n = 119) were available.

The ORs increased as class of asbestos exposure increased from possible to definite exposure, but the possible and probable classes were similar for the cancer and medical control combined dataset and for the medical controls alone. ORs for only three categories of nature of asbestos exposure are presented in the table, namely, Occupational (shown in Table IV as direct or indirect Occupational), Environmental (Table IV Environmental mining) and ''Risk'' occupation. ORs could not be calculated for the other categories due to the small number of cases in these categories (Table IV). Working in a ''Risk'' occupation without recall of exposure was significantly associated with mesothelioma only in the dataset with both medical and cancer controls — the other analyses produced a lower 95% CI of less than 1. It is notable that working with asbestos cement (relative to no asbestos exposure) was strongly associated with mesothelioma in all three datasets. There were no exclusively E Transvaal cases; ORs could not, therefore, be calculated. Even short contact with crocidolite (<2 months) was associated with a fairly substantial relative risk of mesothelioma in the cancer + medical control dataset (OR = 20.7) and in the medical control dataset (OR = 31.9).

## DISCUSSION

This study confirms the importance of environmental exposure in the crocidolite mining area of the NW Cape (now Northern Cape Province), the relative paucity of diagnosed cases linked to amosite, and the rarity of chrysotile cases. Results are consistent with the view that there is a fiber gradient in mesotheliomagenic potential for South African asbestos with crocidolite > amosite > chrysotile.

In the main, limitations of this study relate to representativeness of cases and possible misclassification of exposure. The number of cases who should have entered the study is not known, but indirect evidence suggests that ascertainment of diagnosed cases was reasonable: the only incidence study in South Africa [Zwi et al., 1989] registered 169 cases per year on average for 1980–1984. (This was for the whole of South Africa and histologic confirmation of the diagnosis was not necessary.) More importantly, there is evidence that the 123 cases who entered our study misrepresented South African cases in some respects. Fifty-five percent of the cases were white, yet this group makes up only about 20% of South Africa's population. Poorer access to health care by black South Africans is a likely explanation [Zwi et al., 1989], but the effect of this underrepresentation of black subjects is unknown. No study team was successfully established in Durban (KwaZulu-Natal Province), but Durban has a major harbor which exported asbestos (mainly chrysotile). The proportion of cases collected in Kimberely (22/123) was not as large as expected, given the historic importance of this region. A proportion of suspect cases was diagnosed clinically and not confirmed by pleural biopsy; they were thus not included in the study. In summary, although it cannot be quantified, it is possible that this series of cases underrepresents cases with environmental exposure to Cape crocidolite and those with harbor-related exposure.

A number of strategies were adopted in this study to limit misclassification of exposure. A variety of indicators suggest that this was successful: the high rate of reported asbestos exposure in cases points to good detection of exposed subjects; no subject classified in the unlikely exposure class had coated fibers in the sputum, and 19 of the 20 subjects with coated fibers were classed definite or probable — the remaining subject, classed possible, had worked in a ''Risk'' occupation for 38 years; the very similar exposure profiles in the two sets of controls militates against marked bias in exposure classification. The similar ORs for the possible and probable exposure classes, particularly in the medical controls (seen in Table VII) suggest a lack of distinction between possibly and probably exposed. One explanation for the poor distinction may be the 12-month boundary used to separate possible and probable exposure consequent on spending time in an asbestos mining district (Table I).

### Environmental Cases

The large proportion of cases with purely environmental exposure is unique to South Africa. Australia is the only other country to have mined crocidolite in significant amounts and it has maintained a mesothelioma surveillance program since 1979. Ferguson et al. [1987] presented exposure data on 726 cases collected from 1/1/1980 to 12/31/1985. Environmental exposure had occurred in 43 of these cases (6%) and in only six of these (less than 1%) was environmental exposure due to residence in an asbestos mining region (Wittenoom, the crocidolite district). This is about one case per year — a sharp contrast to the findings of this study. Other mining countries do not report environmental mesothelioma to any extent; for example, McDonald and McDonald [1980] examined the exposure histories of 480 cases of mesothelioma in the USA and Canada. Neighborhood exposure (i.e., exposure recorded as exclusively residence within 20 miles of a chrysotile mine) was found in one USA case and in none of the Canadian cases.

### Fiber-Specific Data: Relative Importance of the NW Cape and Paucity of Chrysotile Cases

In all study centers the majority of cases who had spent time in an asbestos mining district had done so in the NW Cape. The majority of cases who had mined asbestos had mined NW Cape crocidolite (Table V) and the majority of cases with asbestos exposure exclusively in an asbestos mining district had this exposure in the NW Cape (Table VI). Of the 22 cases with only environmental exposure, 20 (91%) were exposed in the NW Cape.

Besides a greater mesotheliomagenic potential of NW Cape crocidolite, explanations for this preponderance of cases with NW Cape mining district experience are: these districts mined much more asbestos than the other districts; the nature of the mining operations led to contamination of a much larger area; and they generated much more dust, thus exposing more people to more dust.

The first suggestion is the easiest to examine. As shown in Table VIII, it was only in about 1960 that crocidolite production exceeded that of amosite, and amosite and chrysotile production was substantial throughout the 1960s

**TABLE VIII.** Asbestos Production and Estimated Number of Miners by Fiber Type South Africa 1940–1975

**Asbestos production[a] 1940–1955 in kilotons, 1960–1975 in metric kilotons**

| | 1940 | 1945 | 1950 | 1955 | 1960 | 1970 | 1975 |
|---|---|---|---|---|---|---|---|
| Cape crocidolite | 7 | 8 | 15 | 35 | 71 | 137 | 165 |
| Amosite | 18 | 17 | 42 | 50 | 62 | 97 | 88 |
| Chrysotile | | | | | 27 | 53 | 100 |

**Number of asbestos miners (% of all asbestos miners)**

| | 1960 | 1970 | 1975 |
|---|---|---|---|
| Cape Crocidolite[b] | | 12,000–14,000 | |
| Amosite[b] | | 7,000 | |
| Chrysotile[c] | 2,600 (17) | 1,200 | 1,500 |

[a]Source of data, 1940–1955 Webster, 1973; 1960–1975 Hart, 1988.
[b]Source of data, Felix et al., 1994.
[c]Source of data, du Toit, 1993.

and early to mid 1970s. (Given the long latent period for mesothelioma, more recent data are not of real interest.) Twenty-seven, 53, and 100 metric kilotons of chrysotile were produced in 1960, 1970, and 1975, respectively [Hart, 1988].

It is true that NW Cape crocidolite mining took place over a wide geographic area, but extensive contamination of the NE Transvaal has been well documented [Felix et al., 1994]: pollution by asbestos of surrounding villages and the environs was extensive (for example, at least nine mills operated in the Mafefe district, each with a large asbestos waste dump), and disease due to environmental exposure was common in mining areas (for example, 389 of 611 randomly selected adults from Mafefe had a history of environmental asbestos exposure and 34% of these 389 individuals had pleural disease). E Transvaal (now Mpumalanga) chrysotile communities have not been studied; the extent of environmental pollution experienced by these communities and of asbestos-related disease in them is not known.

Dust levels in and around NE Transvaal mines and mills were very high (dust counts taken in the Penge mill remained well above 12 fibers/ml until after the second half of the 1970s) [Felix et al., 1994]. Published studies of fiber levels in E Transvaal chrysotile mines are sparse; the only readily available data are from Slade's thesis [1931]. The thesis provides convincing evidence of uncontrolled dust levels (the concentration of dust in the atmosphere was such that objects were rendered indistinguishable at a distance of a few yards) and of high disease rates (of 100 chrysotile mill workers examined, 74 had an abnormal finding consistent with asbestosis [Felix et al., 1994]).

Given the contamination of mining regions in the NE Transvaal and that the NW Cape is a sparsely populated region, it is untenable that the preponderance of NW Cape cases can be explained merely by a preponderance of individuals exposed in the NW Cape.

ORs could not be calculated for cases exposed to only chrysotile, since no such cases were identified, but Table VII shows larger relative risks for environmental exposure in the NW Cape than in the NE Transvaal. The large relative risks associated with Cape crocidolite mining, insulation work, and work with asbestos cement products is notable. The asbestos fiber type to which subjects were exposed in the latter two work situations cannot be determined with confidence from the questionnaire information.

## Paucity of Chrysotile Cases

No case with a history of chrysotile mining entered the study, nor did a case with exclusively environmental exposure to chrysotile. Although no case could be said to have had good evidence of exclusively chrysotile occupational exposure, two reported contact with this material, and little if any work with amphiboles. One of these spent 369 months in chrysotile mining districts and 3 months at an asbestos mine in the NE Transvaal — he had amphiboles isolated from pleural biopsy tissue. The other case is intriguing: despite repeated questioning for clinical and compensation purposes, the only historical source of asbestos exposure was to chrysotile, which began only 4 years prior to diagnosis. This is a very short latent period and does not lend itself to causal interpretation. An amphibole, probably tremolite, was seen in pleural material examined by scanning electron microscopy; this may have been a contaminant of the chrysotile to which she was exposed.

This absence of South African chrysotile cases is not an isolated finding. Mesothelioma cases from South African chrysotile mines have not been recorded [Wagner, 1986].

One explanation for the absence of exclusively chrysotile cases is that production and use of the material in South Africa was so limited that the small number of exposed individuals has resulted in a paucity of cases. This seems unlikely, as is shown in Table VIII. Hart [1988] estimates chrysotile production at about 30% of total asbestos production by the end of the 1970s. In the early 1960s, production was closer to 20% [Hart, 1988]. Substantial numbers of miners worked in chrysotile production: from the 1930s to mid-1980, roughly 1,000 to 2,000 workers were employed in chrysotile mining at any one time (personal communication, du Toit, NCOH, 1991 RdT 16.27), and about 2,600 in 1960, which was 17% of asbestos miners. It seems unlikely from these data that scarcity of exposed workers is an adequate explanation for the absence of cases. Adequate dust control on chrysotile mines during the 1950s, 1960s, and 1970s is another possible reason, but this is intuitively unconvincing. It is notable from Table VIII that the estimates of chrysotile miners are disproportionately small relative to the tonnage mined and amphibole miners. Different mining techniques may be one explanation.

There are suggestive data that Southern African chrysotile contains relatively little tremolite [Rees et al., 1992], which may be an explanation for the paucity of chrysotile cases in the region. These data are preliminary, as they are based largely on a small study of lung fiber content of four ex-miners with asbestos-related disease and asbestos mining exposure exclusively in chrysotile mines. Confirmatory studies are required.

In summary, the great preponderance of crocidolite cases followed by amosite and then chrysotile cases (in this study, no convincing case was identified) is consistent with the view that there is a fiber gradient in mesotheliomagenic potential (crocidolite > amosite > chrysotile). This South African experience of a preponderance of crocidolite cases without convincing chrysotile cases may not be shared in countries with different asbestos mining and usage profiles [Smith and Wright, 1996]. Roggli and colleagues [1993] used scanning electron microscopy to examine fiber type in 94 cases of mesothelioma; amosite was identified in 81% of samples, chrysotile in 21%, and crocidolite in only 16%. The authors conclude that the results do not support the notion that most mesotheliomas in the United States are due to crocidolite asbestos. The country of origin of the chrysotile might be a determinant of the relative contribution of each fiber type to country-specific case-loads. Lippman [1994] has summarized the mesothelioma yields in rat inhalation studies and found them to be highly dependent on fiber type. The percentage of mesotheliomas was 0.6% (1/169 rats) for Zimbabwean chrysotile, 2.5% (13/520) for the various amphiboles as a group, and 4.7% (9/193) for Quebec chrysotile. Supporting this view of a greater risk of mesothelioma following chrysotile exposure are reports of mesothelioma in cases whose lungs contain chrysotile but no amphiboles [Langer and McCaughey, 1982; Moringa et al., 1989; Maltoni et al., 1990; Rogers et al., 1991]. A number of recently published studies of almost exclusively chrysotile-exposed workers have shown high risks of mesothelioma. Raffn and colleagues [1993] reported on 269 men heavily exposed to asbestos and almost exclusively to chrysotile. The relative risk for mesothelioma was 22.73 for workers who had been employed at the facility for 20 or more years. Thus, findings in South Africa may need to be generalized to other settings with caution.

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## APPENDIX

### Memory “Joggers” Read Out to Study Subjects

1. Have you ever been involved in any of the following?
   A. Insulation work
   B. Working with furnaces
   C. Manufacturing asbestos cement products
   D. Working with boilers
   E. Wearing heat protective clothing
   F. Selling asbestos
   G. Construction site work
   H. Demolishing buildings
   I. Working in a factory using asbestos
   J. Working for the navy/Merchant navy
   K. Repairing/servicing motor vehicles more than once a month
   L. Helping manufacture asbestos-containing articles
   M. Working in a power station
   N. Working with the manufacture of batteries
   O. Working in the plastic industry
   P. Using asbestos rope or asbestos gaskets
   Q. Working in the rubber industry
   R. Manufacturing brake linings or clutch plates
   S. Transporting asbestos
   T. Working for a railway company
   U. Insulation of hot water pipes
   V. Working with steam locomotives (train engines)
   W. Working with sugar-cane

2. Did you ever work as a . . . . . . . . ?
   A. Boiler maker
   B. Fitter and/or turner
   C. Stevedore
   D. Marine/civil engineer
   E. Plumber/plumber’s assistant
   F. Welder/welder’s assistant
   G. Building carpenter/building carpenter’s assistant
   H. Electrician/electrician’s assistant
   I. Paint manufacturer