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Malignant mesothelioma — clinical and epidemiological features

A report of 80 cases

K. SOLOMONS

Summary

The clinical and epidemiological features of 80 cases of malignant mesothelioma (as proved by examination of biopsy specimens) referred to the clinic at the National Centre for Occupational Health between January 1977 and June 1983 are reviewed. There was a positive history of asbestos exposure in 89% of cases. The mean survival time from diagnosis to death was 8,6 months and from the onset of symptoms to death 13,6 months. Survival time was unaffected by stage of the tumour, treatment, histological features, smoking status, presenting symptoms, presence or absence of effusion and asbestosis, side of the lesion, source of exposure and lag period from first exposure to diagnosis. The duration of survival was significantly affected by age at diagnosis, duration of asbestos exposure and the number, rather than the type, of treatment regimens used. Caution is advocated in interpreting these data since the number of cases was small and the study design was retrospective. A reference group of 546 cases notified over the same period was drawn from the records of the South African Asbestos Tumour Reference Panel. The incompleteness of national mesothelioma incidence data was noted, and an incidence figure of 7,2 per million per year was calculated from the best-available data for South Africa. This figure is an underestimate because not all diagnosed cases are reflected and, more important, significant numbers of cases are never diagnosed. The extent to which the compensation machinery functions is mentioned.

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Department of Occupational Medicine, National Centre for Occupational Health, Johannesburg
K. SOLOMONS, MB CHB

South African mines produced 249 187 metric tons of asbestos in 1979, of which 53% was crocidolite, 31% chrysotile and 16% amosite. Exports accounted for 95% of the total production, the remaining 5% being used locally. While the 12 050 miners (Table I) who mined this tonnage are at risk of developing asbestos-induced diseases, it is not possible at present to estimate the numbers of people in the rest of the population who are at a similar risk from either occupational or environmental exposure.

Almost 100 new cases of mesothelioma are confirmed nationwide by the South African Asbestos Tumour Reference Panel (referred to as the Panel) each year. This figure, which excludes asbestos tumours other than pleural and peritoneal mesotheliomas, underestimates the true incidence of mesothelioma in the country.

TABLE I. ASBESTOS MINING DATA

	Miners*			Asbestos production (metric tonnes)				
Year	Total	White	Coloured and Black	Total†	Amosite‡	Chrysotile‡	Crocidolite‡	Value† (R1 000)
1977	23 367	1 096	22 271	380 164	—	—	—	137 779
1978	13 311	718	12 593	257 325	—	—	—	121 682
1979	12 050	678	11 372	249 187	39 058	91 828	118 301	107 048
1980	12 626	706	11 920	276 734	—	—	—	102 148
1981	11 316	617	10 699	235 943	56 834	76 772	102 337	117 335
1982	10 724	649	10 075	—	—	—	—	—

Bulletin of Statistics Pretoria Central Statistical Services, 1979, 1982, 1983
†*South African Statistics* Pretoria Central Statistical Services, 1982 11 7
‡*South African Mining and Engineering Yearbook* Johannesburg Jim Emery, 1981 16, 1982 21

Most cases diagnosed in the Johannesburg/Witwatersrand area are referred for an asbestos-exposure history to the clinic attached to the National Centre for Occupational Health. Between 1972 and June 1983 150 documented cases of mesothelioma were seen at the clinic. A report on the first 70 cases was published by Cochrane and Webster[1] in 1978. This article reviews the findings in the subsequent 80 cases. The objectives of the review are to examine the epidemiology of mesothelioma in South Africa and the value of clinical and epidemiological features as prognostic indices for survival.

Subjects and methods

All cases of malignant mesothelioma proven histologically from biopsy specimens and seen by the clinic between January 1977 and June 1983 were included in the study group. Data on each subject were collected from the clinic's files. Where the records were incomplete, additional data were obtained from general practitioners, thoracic surgeons, hospitals, the Panel, the Workmen's Compensation Commissioner, the South African Transport Services, the Medical Bureau of Occupational Diseases, employers and family members. All cases of mesothelioma confirmed by the Panel over the same period, excluding those in the study group, were also evaluated. Only basic data on age, sex, race and exposure history were available for this group and they were not followed up for survival data. The function of this reference group was to act as a body to which clinical findings in the study group could be generalized, if it resembled the study group in significant features, and to provide a broader population from which epidemiological data could be gathered. Diagnosis was either made by the Centre's pathologists or subsequently corroborated by them. The tumour type and the presence or absence of parenchymal asbestosis were also determined on histological examination of biopsy material which was usually obtained at open thoracotomy. Asbestos-exposure histories were taken from all patients or their families at the request of the attendant thoracic surgeon or the Centre's pathologists. Exposure history was considered positive if the patient recalled working with or being environmentally exposed to asbestos. Environmental exposure included childhood, domestic, neighbourhood or any other definite exposure which was not occupational. Possible exposure was recorded if the patient had no recall of specific asbestos exposure, but when he/she had either worked in an industry or spent time in an environment where asbestos contamination was likely. Exposure was considered negative if neither positive nor possible exposure were recorded. Negative exposure means that no exposure history was elicited, not that exposure had never occurred; exposure could have occurred in infancy or childhood, or been negligible or obscure.

Patients were staged retrospectively from data obtained from surgeons' operative findings and notes at the time of diagnosis, according to the system advocated by Mattson[2] (stage I — ipsilateral pleura and lung only; stage II — chest wall invasion, mediastinal or pericardial involvement, contralateral lung or pleural involvement; stage III — extrathoracic extension: (a) nodes outside chest, (b) diaphragmatic penetration to peritoneum; stage IV — distant metastases). It must be emphasized that staging was not an active process and that no standard staging system was used by the different surgeons. Treatment was broadly divided into the major modality used rather than specific agents and regimens since these varied widely, largely because treatment was not carried out at a single centre with standardized regimens.

The data were analysed statistically by a variety of techniques including analysis of variance and product-limit survival analysis. Percentages have been rounded off to the nearest point.

Results

The study group comprised 80 subjects. The mean age at the time of diagnosis was 57,2 years and the range 24 - 87 years. The male : female ratio was 10:1, the group consisting of 73 men (91%) and 7 women (9%). There were 64 Whites (80%), 13 Blacks (16%) and 3 Coloureds (4%). One subject had a primary peritoneal mesothelioma, but the pleura was the primary site in the rest. These mesotheliomas arose on the left side in 37 cases (46%) and on the right side in 40 (50%). No data were available in the remaining 2 cases. In 72% of cases (58/80) the Panel had confirmed the diagnosis of malignant mesothelioma; 3 patients had never been submitted and 19 patients had been submitted but not yet examined (since submission of this article the diagnosis of mesothelioma was confirmed by the Panel in these latter 19 patients).

A positive history of previous asbestos exposure was obtained from 71 subjects (89%); 4 (5%) gave a history of possible exposure and in 5 (6%) no history of prior exposure was elicited. Similar studies in the past have found between 18% and 97% positive asbestos-exposure histories.[3] In 59 cases (74%) there was a history of only occupational exposure, 7 (9%) had a history of only environmental exposure and 5 (6%) had a history of both occupational and environmental exposure. The remaining 9 (11%) had either no exposure or only possible exposure. The 4 subjects with possible exposure had possible occupational exposure, one as a boilermaker, another as a fitter and turner on naval ships, one handling construction material and the fourth as a market agent handling hessian sacks which had previously been used to transport asbestos.

Among those 68 subjects with occupational exposure, 15 (22%) were exposed in the mining industry, 15 (22%) on the

exposure of between 30 and 40 years survived for a mean of 22,1 months whereas patients with less than 1 year's exposure survived for a mean duration of 5,6 months ($P = 0,03$). This difference disappeared when survival was measured from the onset of symptoms ($P = 0,29$).

Patients treated with one or more anticancer modalities survived significantly longer from diagnosis than untreated patients ($P < 0,0001$). While patients treated with four modalities survived significantly longer than patients treated with one or three modalities ($P = 0,01$ and 0,03 respectively), they had no advantage as regards survival over patients treated with two modalities ($P = 0,08$). All these differences, however, disappeared when survival was measured from the onset of symptoms.

The number of cases was too small to permit testing of the effects of combinations of factors such as stage and treatment or stage, treatment and histological type on outcome. This drawback restricts the interpretation of both negative (stage and therapy) and positive (age and therapeutic modalities) associations

The study group resembled the reference group with regard to age (57,2 years and 55,1 years, $P = 0,16$) and histological type of tumour ($P = 0,21$), but had significantly more Whites (80% compared with 43%, $P < 0,0001$) and fewer females (9% compared with 26%, $P = 0,0006$) than the reference group. Furthermore, fewer subjects in the study group were exposed environmentally (9% compared with 30%) and through mining (22% compared with 46%), but a higher proportion were exposed in industry (60% compared with 23%).

These differences are explained by the fact that the study group came mostly from the industrial sector of the Witwatersrand, whereas the reference group was drawn from a nationwide selection and particularly included the populations at risk because of asbestos mining. Mining places large numbers of people at risk, especially women and children through environmental contamination. Thus 52 of the 71 women (73%) in the reference group with known exposure sources were exposed environmentally, and more than half of those exposed environmentally were women (57% as opposed to 43% of the men). It is not possible to comment on the clinical implications of these epidemiological features since the numbers in the study group were too small to indicate the effect, if any, that the source of asbestos exposure might have on survival.

Discussion

Mesothelioma is a rare tumour. Its incidence has been reported as 1 and 2,2/million per annum in Canada and the USA respectively.[5,6] The reporting of cases in South Africa is unfortunately unreliable. Mesothelioma was only coded separately as a specific cause of death by the Department of Statistics in 1977. In 1978 a total of 5 deaths were officially recorded as due to mesothelioma; in the study group alone 4 deaths occurred in that year. The most recent official data available on causes of death are dated 1978 for Whites, Coloureds and Asians (with 4 deaths from mesothelioma, all in Whites) and 1979 for Blacks (in which year 18 deaths from mesothelioma were recorded).[7-9]

In these circumstances the most reliable mesothelioma incidence data at present come from the Panel records. Unfortunately not even the Panel records all diagnosed mesothelioma cases since there is no statutory obligation for cases to be reported to the Panel or any other centre. Over the 3-year period 1980 - 1982 only 57 of the 78 mesothelioma cases diagnosed (and compensated) by the Medical Bureau for Occupational Diseases were reported to the Panel (unpublished records of the MBOD, 1980 - 1983). In addition to these 21 unreported cases, there are 3 from the study group which were also not reported to the Panel.

There is also cause to believe that significant numbers of cases occur which are never diagnosed, particularly among Blacks.[1] These unrecognized cases contribute further to the extent whereby the best-available figures underestimate the true incidence. The total number of miners in the study and reference groups, including the 21 miners from the Medical Bureau for Occupational Disease records, is 171. Of these 44 (26%) were White, 40 (24%) Coloured and 87 (51%) Black. The White to Coloured and Black ratio is therefore almost 1:3. The race distribution of asbestos miners for the period 1977 - 1982 averaged 1 White to nearly 18 Coloureds and Blacks (Table I). The number of Coloureds and Blacks at risk from asbestos mining exposure is therefore nearly 18 times the number of Whites. Since the average duration of employment of Black miners is shorter and their rate of turnover higher than those of the White miners, it is likely that greater numbers and an even higher proportion of Black miners are at risk.

While the evidence for a dose-response relationship for mesothelioma is not as strong as it is for lung cancer in relation to asbestos exposure, it is reasonable to assume that people with shorter durations of exposure have a lower relative risk of contracting mesothelioma than those with longer exposures.[10] However, most South African asbestos miners work on the mines for longer than 2 - 3 months and would therefore have an exposure greater than 2 - 3 fibre-years/ml, a level which Nicholson *et al.*[10] regard as sufficient to impart a significant risk for the development of asbestos disease. It is beyond the scope of this article to estimate the size of the at-risk population in South Africa or to put a figure to the true incidence of mesothelioma, but it is clear from the above discussion that in spite of the relatively large numbers of Black miners found to have mesothelioma, significant numbers of cases must occur which are never recognized or diagnosed. The extent of underdiagnosis is probably more marked in the non-mining industries. Of all the mesotheliomas arising from non-mining industry, 87% occurred among Whites and only 13% among Coloureds and Blacks. The ratio of Blacks to Whites is not as high in non-mining industry as in the mining industry, but is still high enough to expect that greater numbers of mesotheliomas would occur among Coloured and Black workers. The Black : White ratio in the two industries where most non-mining mesotheliomas arose in this study, the construction industry and the railways, is 6,5:1 and 1,3:1 respectively.[11] A similar situation applies as regards the environmentally exposed cases where 45% of all cases detected occurred among Whites and 55% among Coloureds and Blacks.

From the mean figure of 96,3 new cases of mesothelioma per year found in this study, an annual incidence figure, age-adjusted to the 1980 US population, of 7,2 per million population was derived (Table V). As has been shown, even this figure underestimates the true incidence — further research is needed to arrive at more reliable estimates. The most plausible explanation for the South African incidence being more than three times higher than that found in the US is that asbestos is not mined or milled there in any major quantity, whereas these activities are central to the South African asbestos industry The Canadian incidence rate is much lower than the South African rate, presumably because although much mining and milling is carried out in Canada, only chrysotile is worked in Canada whereas South Africa mines crocidolite and amosite as well, both of which are considered to be more carcinogenic in man than chrysotile.[3]

Another area of interest in the context of mesothelioma in South Africa is compensation. Mesothelioma was made an occupational disease, sufferers of which were eligible for compensation in the non-mining sector, in 1979, although it has been compensated in the mining industry under a provision for compensation of pneumoconiosis since 1962. In this series of 48 industrially exposed non-mining subjects, fewer than half (38%) of all those eligible have been compensated. The situation in the mining industry is much better and 88 subjects were compensated by the mines over the study period. Even so only 1 of the 8 Black miners from the study is known to have been compensated to