PLAINTIFF'S EXHIBIT

SA-489

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

The International Agency for Research on Cancer (IARC) was established in 1965 by the World Health Assembly, as an independently financed organization within the framework of the World Health Organization. The headquarters of the Agency are at Lyon, France.

The Agency conducts a programme of research concentrating particularly on the epidemiology of cancer and the study of potential carcinogens in the human environment. Its field studies are supplemented by biological and chemical research carried out in the Agency's laboratories in Lyon and, through collaborative research agreements, in national research institutions in many countries. The Agency also conducts a programme for the education and training of personnel for cancer research.

The publications of the Agency are intended to contribute to the dissemination of authoritative information on different aspects of cancer research. A complete list is printed at the back of the book.

This volume contains the proceedings of a symposium held on 8-10 September 1987 in Lyon, and organized jointly by:

International Agency for Research on Cancer

WHO Regional Office for Europe

International Programme on Chemical Safety

Commission of European Communities

French Ministry of the Environment (Service de la Recherche des Etudes et de Traitement de l'Information sur l'Environnement)

Cover illustration: Scanning electron micrographs of crocidolite, glass wool, basaltic glass fibre and sepiolite samples after various treatments (see pp. 134-139). Reproducted by permisson of G. Larsen.

WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

Non-occupational Exposure to Mineral Fibres

Edited by

J. Bignon, J. Peto and R. Saracci

IARC Scientific Publications No. 90

International Agency for Research on Cancer, Lyon, France

1989

ASBESTOS FIBRE CONTENT OF LUNGS WITH MESOTHELIOMAS IN OSAKA, JAPAN: A PRELIMINARY REPORT

K. Morinaga[1], N. Kohyama[2], K. Yokoyama[3], Y. Yasui[4], I. Hara[4], M. Sasaki[5], Y. Suzuki[6] & Y. Sera[3]

[1]*Department of Field Research, Center for Adult Diseases, Osaka, Japan*
[2]*Ministry of Labor, Institute of Industrial Health, Kawasaki, Japan*
[3]*National Kinki-Chuo Hospital for Chest Disease, Sakai, Japan*
[4]*Department of Public Health, Kansai Medical University, Moriguchi, Japan*
[5]*Department of Pathology, Osaka Red Cross Hospital, Osaka, Japan*
[6]*Environmental Sciences Laboratory, Mount Sinai School of Medicine, New York, NY, USA*

Summary. That crocidolite and amosite are both associated with the development of mesothelioma is now well established, but earlier studies have failed to find an excess of chrysotile in lungs with mesotheliomas as compared with the amounts in lungs of unaffected controls. In an attempt to clarify the importance of fibre type in tissue, an examination of a series of mesotheliomas is being undertaken in Osaka, Japan. A total of 23 mesotheliomas and 5 rejected cases reviewed by the Osaka Mesothelioma Panel were examined for the types of asbestos and semiquantitative fibre content by means of a transmission electron microscope equipped with energy-dispersive X-ray analyser. Asbestos fibres were detected in 19 of the 23 mesotheliomas (21 pleura, 1 pericardium, 1 peritoneum; 19 males, 4 females). Amphibole fibres were found in 13 cases. Five pleural and one peritoneal mesothelioma were found to have only chrysotile fibres. One female pleural mesothelioma with neighbourhood exposure had short chrysotile fibres. Among the 5 rejected cases, only one case with occupational exposure had both chrysotile and amosite fibres. A group of 17 controls were also examined and asbestos fibres were found in 5. Our data, while not definitive, suggest that mesotheliomas can be induced in humans, not only by crocidolite and amosite, but also by chrysotile, though possibly to a lesser extent.

Introduction

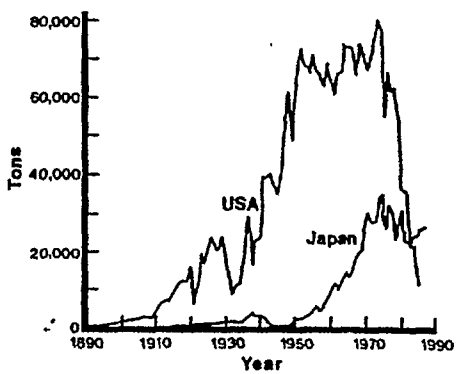
In Japan, only one chrysotile mine is in operation and it produces about 1500 tons of low-grade asbestos annually. Almost all asbestos used in Japan therefore comes from foreign countries (Table 1). The import of raw asbestos to Japan has increased since the 1950s and reached about 300 000 tons in the 1970s, which exceeded US total consumption in 1983 (Figure 1).

Osaka, which is the second largest commercial and industrial urban area in the country, has the largest number of asbestos factories and produces about one-third of all asbestos in Japan. Judging by the number of death certificates and cancer registry

Table 1. Asbestos imports in Japan in 1965 and 1985

Country	Imports (tons)	
	1965	1985
Canada	71 767	102 979
South Africa	35 731	57 955
USSR	15 032	45 493
USA	10 031	10 780
Australia	890	3
Zimbabwe	–	29 253
Italy	–	7 414
Greece	–	6 152
Others	363	1 622
Total	146 294	261 648

Fig. 1. Annual US consumption of asbestos from 1890 to 1986 and annual Japanese asbestos imports from 1913 to 1986



cards notified as mesothelioma, the mortality from this condition has been increasing together with the number of death certificates mentioning asbestosis (Table 2). To ascertain incidence rates of mesotheliomas and to assess the relationship of this

tumour to asbestos, the Mesothelioma Register and Panel was started in 1980. This is the first report from Japan on the types of asbestos in lungs with mesotheliomas.

Table 2. Death certificates and cancer registry cards mentioning mesothelioma and asbestosis, Osaka, 1967–1985

Year of death	Death certificates mentioning mesothelioma	Registry cards mentioning mesothelioma	All certificates mentioning asbestosis
1967	1	4	1
1968	0	4	2
1969	1	2	1
1970	0	3	4
1971	4	6	1
1972	1	4	6
1973	2	4	1
1974	3	5	4
1975	1	3	5
1976	6	8	5
1977	4	6	3
1978	4	8	6
1979	9	12	7
1980	4	9	3
1981	7	11	8
1982	13	20	5
1983	9	16	7
1984	10	15	9
1985	11	13	5

Materials and methods

From June 1981 to October 1986, 49 autopsied cases were reviewed by the Osaka Mesothelioma Panel in the same way as described by Kannerstein *et al.* (1979). A total of 33 cases were classified as definite or probable mesotheliomas, 2 possible, and 14 unsubstantiated. Blocks of tissues were requested to be more than 2×2×2 cm in size and were collected from 23 mesotheliomas and 5 rejected cases. In each case, 2 controls matched for hospital, age and year of death were obtained from a case of lung cancer and one of a non-respiratory disease. For mesotheliomas and rejected cases, lung tissue was obtained from the middle basal area of the unaffected lower lobe, and for controls, tissues from the same area of the same-side lower lobe were used. They were embedded in paraffin and cut into several serial sections of thickness 20 μm. After deparaffinization in xylene, those specimens were ashed at low temperature and transferred on to a nickel grid by a carbon extraction technique. The specimens were examined by one of the authors (N.K.) using a Hitachi H-500 transmission electron

microscope fitted with a Kevex model 5100 energy-dispersive X-ray analyser. Asbestos types were identified by their characteristic morphologies, chemical composition and electron diffraction patterns. The amounts of asbestos fibres observed were graded as follows: (+++) dozens of fibres observed in almost all areas arbitrarily selected under low magnification (5000–10 000) in the microscope; (++) 10 or so fibres on average detected in every 2 or 3 areas; (+) a few fibres found in the entire specimen; (-) no fibres detected. A fibre was defined as a particle having an aspect ratio of 3:1 or greater.

Results

The results obtained are shown in Table 3. All the mesotheliomas, 17 controls, and the 5 rejected cases were examined to determine the mineral fibre content (see Table 4). Asbestos fibres were frequently found in mesotheliomas (19/23), but infrequently in the control series (5/17). Amounts of asbestos fibres graded as (++) or (+++) occurred only in the mesothelioma series except for one rejected case with occupational exposure, which was correctly diagnosed as peripheral lung carcinoma. Five cases were graded (+) or (+~++) in the control series; of these, 3 were lung cancer patients, whose occupations had been farmer, housewife and part-time office worker. The other 2 controls were a farmer who had died of myocardial infarction and a man with renal cancer who had worked for a delivery service company. Table 5 shows the data on types of asbestos in the study series. Amphiboles were detected in 13 mesotheliomas, of whom 3 had been shipbuilders, 3 had been employed in a plant which manufactured asbestos products, 2 in a factory which made railway carriages, and a chemical engineer who had been intermittently exposed to asbestos while replacing boiler insulation. The remaining 4 were 3 clerks and one worker employed in a plant which manufactured light bulbs; it is not known whether or not they had a history of asbestos exposure. Four controls and one rejected case also had amphiboles, while 6 mesotheliomas were found to have chrysotile only (Table 6). One plastic factory worker with occupational exposure was graded (+++) and had long, thin chrysotile fibres, while a housewife living near an asbestos factory was graded (+~++) and had short chrysotile fibres. The latent period in her case from initial neighbourhood exposure to detection of the disease was 35 years. We could not ascertain whether the design engineer and the surgeon had had any contact with asbestos.

Table 3. Number, sex and mean age of cases examined

Series	Men	Women	Total	Mean age (years)
Mesotheliomas	19	4	23	62±10
Controls 1[a]	10	3	13	63±6
Controls 2[b]	11	3	14	62±11
Rejected cases	4	1	5	61±13

[a]Lung cancer.
[b]Non-respiratory disease.

Table 4. Asbestos fibre content in mesotheliomas, controls and rejected cases

Series	Fibre content					
	–	+	+–++	++	+++	Total
Mesotheliomas	4	3	2	4	10	23
Controls 1[a]	5	2	1	0	0	8
Controls 2[b]	7	2	0	0	0	9
Rejected cases	3	1	0	1	0	5

[a]Lung cancer.

[b]Non-respiratory disease.

Table 5. Types of asbestos in the study series

Series	Number examined	Serpentines	Amphiboles[a]		
		Chrysotile	Amo	Cro	Ac-Tr
Mesotheliomas	23	12	13	3	3
Controls 1[b]	8	0	1	1	1
Controls 2[c]	9	1	0	0	1
Rejected cases	5	1	1	0	1

[a]Amo, amosite; Cro, crocidolite; Ac-Tr, actinolite-tremolite.

[b]Lung cancer.

[c]Non-respiratory disease.

Table 6. Clinical, occupational and semiquantitative fibre content data on 6 mesotheliomas having only chrysotile fibres[a]

No.	Age (years)	Sex	Site	Occupation	Fibre content
2	62	M	Pl	Welder	+
8	76	M	Pl	Plater	++
22	69	F	Pl	Housewife	+–+++
26	54	M	Per	Design engineer	+
32	69	M	Pl	Plastic factory worker	+++
38	70	M	Pl	Surgeon	+–++

[a]M, male; F, female; Pl, pleura; Per, peritoneum.

Discussion

An association between malignant mesothelial tumours and exposure to commercial amphiboles is well established. With regard to chrysotile, however, it has been reported (Jones *et al.*, 1980; McDonald *et al.*, 1982; Wagner *et al.*, 1982) that chrysotile fibres were not found to a greater extent in the lungs of mesotheliomas than in those of controls. The deposition and clearance of chrysotile from the lungs are different from those of amphiboles, and chrysotile may disappear more rapidly than amphiboles in the course of time. In addition, the digestion methods commonly used for the preparation of lung tissue specimens may produce a more distorted estimation of the fibre burden of the lung for chrysotile than for amphiboles. Our method of using the ashing technique alone may be useful for differentiating between occupational and non-occupational exposures. Our data show that, if amphibole and/or an amount of chrysotile graded as more than (++) are found, mesotheliomas may be occupationally induced. This is only a preliminary report, but it nevertheless indicates that 32% (6/19) of mesotheliomas found to contain asbestos fibres contained only chrysotile fibres. Of 3 mesotheliomas found to contain actinolite-tremolite, all also had an amount of amosite graded as more than (++). Our study suggests, therefore, that chrysotile can also induce mesotheliomas in humans, but possibly to a lesser extent than crocidolite and amosite. Thus chrysotile may have a larger role in causing mesothelioma than previously found.

Acknowledgements

This study was partly supported by a Grant in Aid for Scientific Research from the Ministry of Education, Culture and Science, Japan. We thank Dr I. Fujimoto, A. Hanai (Osaka Cancer Registry) and the members of the Mesothelioma Study Group for their co-operation in data collection.

References

Jones, J.S.P., Roberts, G.H., Pooley, F.D., Clark, N.J., Smith, P.G., Owen, W.G., Wagner, J.C. & Berry, G. (1980) The pathology and mineral content of lungs in cases of mesothelioma in the United Kingdom in 1976. In: Wagner, J.C., ed., *Biological Effects of Mineral Fibres* (*IARC Scientific Publications No. 30*), Lyon, International Agency for Research on Cancer, pp. 187-200

Kannerstein, M., Churg, J. & McCaughey, W.T.E. (1979) Functions of mesothelioma panel. *Ann. N.Y. Acad. Sci.*, *330*, 433-439

McDonald, A.D., McDonald, J.C. & Pooley, F.D. (1982) Mineral fibre content of lungs in mesothelial tumours in North America. *Ann. Occup. Hyg.*, *26*, 417-422

Wagner, J.C., Pooley, F.D., Berry, G., Seal, R.M.E., Munday, D.E., Morgan, J. & Clark, N.J. (1982) A pathological and mineralogical study of asbestos-related deaths in the United Kingdom. *Ann. Occup. Hyg.*, *26*, 423-431