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Pleural Plaques as Risk Indicators for Malignant Pleural Mesothelioma: A Necropsy-Based Study

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Pleural plaque is recognized as a reliable marker of previous exposure to asbestos. However, it is controversial whether pleural plaque is a risk indicator for asbestos-related malignancies. In the present study, the thoracic cavities were examined for pleural plaques in 3,005 necropsies performed at the Monfalcone Hospital in people aged 15 years or older. Plaques were classified into three classes: 1, small (plaques measuring 1–4 cm in major diameter); 3, large (plaques involving a major part of a hemithorax); and 2, moderate (intermediate conditions). The prevalences of pleural plaques were 70.9% among men, and 24.0% among women. The prevalences of plaques (total plaques, various classes) among subjects with pleural mesothelioma were compared with those observed in the remaining cases. The series included 92 subjects with malignant pleural mesothelioma (82 men and 10 women). Mesothelioma cases showed higher prevalences of total plaques as well as higher prevalences of classes 1, 2, and 3, when compared with controls. These differences reached the statistical significance for total plaques, and classes 2,3. The present data are consistent with the idea that pleural plaque is a risk indicator for pleural mesothelioma. Am. J. Ind. Med. 32:445–449, 1997. *© 1997 Wiley-Liss, Inc.*

KEY WORDS: asbestos; pleural plaque; pleural mesothelioma; risk factors; necropsy studies

INTRODUCTION

The incidence of malignant mesothelioma, a cancer closely related to asbestos exposure, shows a dramatic and progressive increase in many countries [Iwatsubo et al., 1994; Peto et al., 1995; Leigh et al., 1996]. Such an increase has been defined as an epidemic [Huncharek, 1992; Peto et al., 1995]. The proportion of mesotheliomas attributable to asbestos varies considerably, reaching 90–100% in some series [Giarelli et al., 1992; Bianchi et al., 1993].

In identifying and in characterizing asbestos-related cancer, it is critical that the existence of a previous exposure to asbestos as well as the degree of such an exposure might be documented by objective signs. Lung asbestos bodies (and fibers) [Murai et al., 1995] and pleural plaques [Hillerdal, 1980; Järvholm et al., 1986; Chailleux et al., 1988] are well-recognized markers of exposure to asbestos. In particular, pleural plaque has extensively been investigated during the last decades.

Pleural plaques are whitish, sharply circumscribed, fibrous, hyaline, sometimes calcified, patches involving parietal pleura. The relationship between pleural plaque and asbestos exposure has convincingly been proved. Generally, there is a direct relation between the intensity of asbestos exposure and the total area of the pleura involved by the plaques [Bianchi et al., 1991].

Pleural plaques may be detected by various ways: standard chest x-rays, computed tomography (CT), pleuroscopy, thoracotomy, and necropsy.

The meaning of pleural plaques in terms of cancer risk has not been exactly defined [Weiss, 1993; Hillerdal, 1994; Smith, 1994]. In the present study, based on necropsy material, the relationship between pleural plaques and malignant mesothelioma, has been investigated.

Our research has been conducted in the Monfalcone area (northeastern Italy), a small industrial district (about

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TABLE I. Prevalence of Pleural Plaques in a Necropsy Series, Monfalcone Area, Oct. 1979–March 1995

	Pleural plaques, men %					Pleural plaques, women %				
Age (years)	No. of cases	Absent	Small	Moderate	Large	No. of cases	Absent	Small	Moderate	Large
15–29	2	100.0	0.0	0.0	0.0	2	100.0	0.0	0.0	0.0
30–39	25	60.0	8.0	20.0	12.0	13	92.3	7.7	0.0	0.0
40–49	80	35.0	21.3	22.5	21.3	27	92.6	7.4	0.0	0.0
50–59	246	30.5	20.7	25.2	23.6	55	72.7	23.6	3.6	0.0
60–69	445	28.1	27.4	25.8	18.7	151	69.5	23.2	6.6	0.7
70–79	645	26.2	22.6	30.7	20.5	361	72.6	21.3	5.5	0.6
80–89	405	29.1	23.5	28.1	19.3	442	79.2	16.7	3.8	0.2
>90	30	50.0	30.0	13.3	6.7	76	80.3	14.5	5.3	0.0
Total	1,878	29.1	23.5	27.5	19.9	1,127	76.0	18.9	4.7	0.4

60,000 inhabitants), with large shipyards. This area is characterized by a very high incidence of asbestos-related mesothelioma [Bianchi et al., 1993] and by very high prevalences of pleural plaques in the necropsy population [Bianchi et al., 1991].

MATERIALS AND METHODS

From October 1, 1979 to March 31, 1995, 3,041 necropsies were performed at the Monfalcone Hospital. Necropsy rates in this period were 46.5% for males, and 33.9% for females who died at the hospital. All the 3,005 necropsies carried out in the above period on subjects aged 15 years or older were included in the study. In each case, the thoracic cavity was carefully inspected for the presence of pleural plaques. The necropsies were carried out by six pathologists, all of them involved in the research on the prevalence of pleural plaques. Whitish hyaline patches, unilateral or bilateral, calcified or not, involving parietal pleura, were considered as pleural plaques. Histological examination of pleural plaques was performed in the majority of the cases.

Pleural plaques were classified into three classes: 1, small; 2, moderate; and 3, large on the basis of the size of the plaques. Class 1 included the cases with small plaques (1–4 cm in major diameter); class 3 corresponded to cases with large plaques involving the majority of a hemithorax; class 2 comprised the intermediate conditions. When the two pleural cavities differed one from the other (one side only being involved by the plaques, or both sides being involved but at different degrees), the classification of the case was based on the aspect of the involved, or of the more seriously involved, side.

The prevalence of pleural plaques among subjects with malignant pleural mesothelioma was compared with that observed in the remaining cases.

Statistical analysis was performed by Epi Info, version 5, from the Centers for Disease Control (Atlanta, GA). To compare pleural cancer cases with the remaining subjects, Mantel-Haenszel weighted odds ratios with Cornfield 95% confidence limits were calculated, after stratification by age (10-year intervals). When absolute numbers were too low, odds ratios were computed without age stratification, with exact 95% confidence limits. The chi-square test for trend (Mantel extension) was used to compare the crude odds ratios obtained for the various classes of plaques.

RESULTS

The series consisted of 1,878 men and 1,127 women. The prevalences of pleural plaques were 70.9% in men, and 24.0% in women. Pleural plaques were rare among younger people, but their prevalence increased after the age of 30 years in men, and after the age of 50 in women. There were marked sex differences in the distribution of the three classes of plaques (Table I). The prevalence of pleural plaques in malignant pleural mesothelioma is reported in Table II. People with mesothelioma showed higher prevalences of pleural plaques (total plaques, as well as classes 1, 2, and 3). when compared with controls (Tables III, IV). The differences were significant for total plaques and classes 2 and 3.

When the odds ratios obtained for the various classes of plaques were analyzed by the chi-square test for linear trend, highly significant values were observed (Table V).

DISCUSSION

The prevalence of pleural plaques in the general population varies widely, depending on the method employed and on the geographical area investigated [Hillerdal, 1980; Järvholm et al., 1986; Chailleux et al., 1988]. Conventional chest radiography has low sensitivity in detecting pleural

TABLE II. Prevalence of Pleural Plaques in Malignant Pleural Mesothelioma, Monfalcone Area, Oct. 1979–March 1995

	Pleural plaques, men %					Pleural plaques, women %				
Age (years)	No. of cases	Absent	Small	Moderate	Large	No. of cases	Absent	Small	Moderate	Large
40–49	4	0.0	0.0	50.0	50.0	1	100.0	0.0	0.0	0.0
50–59	12	8.3	25.0	16.7	50.0	2	100.0	0.0	0.0	0.0
60–69	23	4.3	30.4	30.4	34.8	1	0.0	100.0	0.0	0.0
70–79	28	14.3	14.3	32.1	39.3	2	0.0	0.0	50.0	50.0
80–89	14	21.4	21.4	21.4	35.7	4	0.0	75.0	25.0	0.0
>90	1	0.0	0.0	0.0	100.0	0	—	—	—	—
Total	82	11.0	20.7	28.0	40.2	10	30.0	40.0	20.0	10.0

TABLE III. Comparison Between Prevalences of Pleural Plaques in Pleural Mesothelioma and Controls (Men), Monfalcone Area, Oct. 1979–March 1995

	Pleural mesothelioma vs controls			
Pleural plaques	MH-weighted OR	MH[a] summary chi-square	*P*	Cornfield 95%CI
Absent	1	—	—	—
Present	3.43	12.7	0.0004	1.71–7.94
Small	2.34	3.59	0.06	0.97–6.04
Moderate	2.70	5.92	0.015	1.20–6.78
Large	5.73	24.49	<0.0001	2.65–13.8

[a]Mantel–Haenszel.

TABLE IV. Comparison Between Prevalences of Pleural Plaques in Pleural Mesothelioma and Controls (Women), Monfalcone Area, Oct. 1979–March 1995

	Pleural mesothelioma vs controls		
Pleural plaques	OR	Fisher exact *P*	Exact 95%CI
Absent	1	—	—
Present	7.58	0.0026	1.71–45.62
Small	5.45	0.032	0.91–37.39
Moderate and large	15.81	0.0040	2.1–119.9

TABLE V. Pleural Plaques in Pleural Mesothelioma Versus Controls Analyzed by Linear Trend Test, Monfalcone Area, Oct. 1979–March 1995

Pleural plaques	Men Crude OR	Women Crude OR
Absent	1.00	1.00
Small	2.39	5.45
Moderate	2.79	15.81
Large	5.80	
Chi-square for linear trend	24.95	16.539
P	<0.0001	<0.0001

plaques. More reliable data are obtained by using CT and high-resolution computed tomography [Ameille et al., 1993]. In routine necropsy series, prevalences of 8.1–44% among men, and 0.5–10.0% among women have been reported [Andrion et al., 1982]. Very high prevalences of pleural plaques were radiologically observed in some areas of Finland [Järvholm et al., 1986], Turkey [Järvholm et al., 1986], and Greece [Costantopoulos et al., 1987; Sichletidis et al., 1992]. The figures found in the present study (70.9% among men, and 24.0% among women) are very high, when compared with the generality of the other necropsy series.

What does pleural plaque mean? In the history of pleural plaque recognition, four steps, or phases (which partially overlapped) may be distinguished. In the first phase, for a long time, pleural plaques were interpreted as late sequelae of tuberculosis. In the second phase, since the early 1960s, the idea did emerge (with difficulty) that pleural plaque indicates a not trivial exposure to asbestos, having occurred some 10–20 or more years previously [Hourihane et al., 1966]. Asbestos-related pleural plaque was initially considered completely devoid of any physiopathological relevance. However, in the third phase, a series of studies performed, especially during the late decade, suggest that radiologically detectable pleural plaques are associated with impairment of pulmonary function [Järvholm and Sandén, 1986; Loomis et al., 1989; Bourbeau et al., 1990; Kilburn and Warshaw, 1990; Kouris et al., 1991]. The fourth phase refers to the relationship of pleural plaques to cancer. The debate on this crucial point has a long history, but the question remains open [Weiss, 1993; Hillerdal, 1994; Smith, 1994]. Given the two clear premises: (1) pleural plaque indicates exposure to asbestos, and (2) asbestos induces cancer in lung and pleura, the logic would suggest the conclusion that (3) pleural plaque is a risk marker for pleural and pulmonary malignancies. Nevertheless, while a few investigations have supported this conclusion, other studies did not confirm it [Weiss, 1993; Hillerdal, 1994; Smith, 1994]. Studies performed on this topic strongly differ among them for a number of features, including the design (cohort studies, case-control studies, necropsy based studies), methods used in detecting plaques (radiology, direct inspection), occupational settings. The impact of these differences is not difficult to appreciate. As far as method of detection is concerned, it has been reported that only 10–40% of the plaques visible at direct inspection are identified by radiology. A major source of variability is represented by occupation. The various occupational settings are difficult to compare among them; people had sometimes been exposed to one type only of asbestos, and more often to various types. This problem is strongly complicated by the fact that often the proportion of the various types of asbestos in a given workplace is not known. Moreover, the oncogenic potential of the single varieties of asbestos is not completely clear [Bianchi et al., 1993].

In the Monfalcone area, the necropsy population shows a very high prevalence of pleural plaques. In this small area, a large majority of the male population has spent some part of his working life in the shipyards. Previous necropsy-based research, conducted at our laboratory [Bianchi et al., 1991], showed that the workers of the Monfalcone shipyards were characterized by very high prevalences of pleural plaques (93.4%), and by high prevalence of asbestos bodies in routine lung sections (42.8%). Isolation of asbestos bodies after digestion of the lung tissue from shipyard workers frequently showed more than 10,000 asbestos bodies per gram of dried tissue. The other occupational groups showed by far lower indexes of asbestos exposure. Overall, our findings showed that in the Monfalcone area, pleural plaques in men were attributable to occupational exposure to asbestos, occurring mostly in the Monfalcone shipyards; in women the main cause was domestic exposure to asbestos, due to cleaning of work clothes, polluted by asbestos.

Necropsy studies are not considered ideal in epidemiology. For instance, necropsy investigations are biased by selection factors. On the other hand, these studies may furnish information, difficult or impossible to obtain by other ways. In the case of pleural plaque, necropsy allows the identification of all the plaques, even if minimal. In addition, the plaques may be classified according to their size; this is very relevant, given the already mentioned relationship between intensity of exposure to asbestos and size of the plaques. Measurement of the total area of parietal pleura involved by the plaque is the best way of evaluating the plaque. Such method, however, is difficult to apply in routine necropsies. A pilot study performed at our laboratory showed that a more rough classification (adopted in the present investigation), may furnish sufficient information [Bianchi et al., 1981]. Another point to be considered is that necropsy allows the identification of all malignancies. Despite major progress in diagnostic techniques, the percentages of clinical misdiagnoses in oncology remain rather high [Lancet, 1994; Lee, 1994; de Pangher Manzini et al., 1995]. In particular, discrepancies between clinical and necropsy diagnosis may reach high levels in the case of malignant pleural mesothelioma [Giarelli et al., 1994].

The present findings indicate a strong relationship between pleural plaque and pleural mesothelioma. In the studies about the relationship between pleural plaques and cancer, both pleural and pulmonary malignancies were often considered. In some studies lung cancer only was investigated. The crucial point in the controversy about this topic is the possible effect of smoking. Since some studies suggest a role of smoking in the development of pleural plaque, some researchers retain that smoking could explain the association between pleural plaque and lung carcinoma.

Pleural mesothelioma, explored in our study, is a condition not related to smoking. In addition, data collected in the Monfalcone area indicate that mesothelioma patients do not differ in their smoking habits from the general population. Therefore, the relationship between pleural plaques and pleural mesothelioma cannot be explained by smoking.

Despite major limitations in the use of asbestos (or total banning of it), the incidence of malignant mesothelioma is increasing in various countries [Bianchi et al., 1993; Peto et al., 1995; Leigh et al., 1996]. In addition, data from Britain suggest that mesothelioma deaths will continue to increase for some decades [Peto et al., 1995]. Prevention of mesothelioma in healthy individuals, exposed to asbestos in the past, is an aim to pursue. Some prospective studies [Hillerdal, 1994] suggest that detection of pleural plaques may allow the identification of people at risk for mesothelioma. The strong association between pleural plaques and mesothelioma, observed in the present investigation, supports such an idea.

While less sensitive than direct inspection in detecting pleural plaques, chest radiography may identify subjects with large or very large plaques, precisely those at higher risk of mesothelioma.

Both pleural plaque and pleura mesothelioma are asbestos-related lesions with long incubation periods. Pleural plaques develop with latencies of 10–20 years; mesothelioma generally requires longer intervals, latent periods frequently being 40 years or over [Bianchi et al., 1997].

Thus, a rather long interval generally separates the ‘‘time of the plaques’’ from the ‘‘time of mesothelioma.’’ Such long interval offers an opportunity for preventive measures, specifically directed to people at risk.

Unfortunately very few data are available at present on this point [Bianchi et al., 1993]. A study conducted some years ago [Schiffman et al., 1988] suggested that consumption of vegetables or some vegetable-related constituent might have a protective effect on the risk of developing mesothelioma. However, the role of cofactors in the pathogenesis of asbestos-related mesothelioma remains largely unexplored. The possibility of identifying a population at risk should represent a further strong stimulus to intensive research in this specific area.

REFERENCES

Ameille J, Brochard P, Brechot JM, Pascano T, Cherin A, Raix A, Fredy M, Bignon J (1993): Pleural thickening: A comparison of oblique chest radiographs and high-resolution computed tomography in subjects exposed to low levels of asbestos pollution. Int Arch Occup Environ Health 64:545–548.

Andrion A, Colombo A, Dacorsi M, Mollo F (1982): Pleural plaques at autopsy in Turin. A study on 1,019 adult subjects. Eur J Respir Dis 63:107–112.

Bianchi C, Brollo A, Miniussi C, Bittesini L (1981): Asbestos exposure in the Monfalcone area. A social and pathological study of 100 autopsy cases. Tumori 67:279–282.

Bianchi C, Brollo A, Ramani L, Berté R (1991): Exposure to asbestos in Monfalcone, Italy. A necropsy based study. In Riboli E, Delendi M (eds): ‘‘Autopsy in Epidemiology and Medical Research.’’ Lyon: IARC, pp 127–140.

Bianchi C, Brollo A, Ramani L, Zuch C (1993): Asbestos-related mesothelioma in Monfalcone, Italy. Am J Ind Med 24:149–160.

Bianchi C, Giarelli L, Grandi G, Brollo A, Ramani L, Zuch C (1997): Latency periods in asbestos-related mesothelioma of the pleura. Eur J Cancer Prev (in press).

Bourbeau J, Ernst P, Chrome J, Armstrong B, Becklake MR (1990): The relationship between respiratory impairment and asbestos-related pleural abnormality in an active work force. Am Rev Respir Dis 142:837–842.

Chailleux E, Rembeaux A, de Lajartre AY, Delumeau J (1988): Pathologie pleurale bénigne de l’amiante. Rev Pneumol Clin 44:166–180.

Costantopoulos SH, Langer AM, Saratzis N, Nolan RP (1987): Regional findings in Metsovo lung. Lancet 2: 452–453.

de Pangher Manzini V, Revignas MG, Brollo A (1995): Diagnosis of malignant tumor: Comparison between clinical and autopsy diagnoses. Hum Pathol 26:280–283.

Giarelli L, Bianchi C, Grandi G (1992): Malignant mesothelioma of the pleura in Trieste, Italy. Am J Ind Med 22:521–530.

Giarelli L, Bianchi C, Grandi G (1994): Asbestos-related mesothelioma of the pleura in Trieste, Italy, In Mehlman MA, Upton A (eds): ‘‘The Identification and Control of Environmental and Occupational Diseases.’’ Princeton, NJ: Princeton Scientific Publishing, pp 343–351.

Hillerdal G (1980): ‘‘Pleural Plaques. Occurrence, Exposure to Asbestos, and Clinical Importance.’’ Uppsala: Acta Universitatis Upsaliensis, 363.

Hillerdal G (1994): Pleural plaques and risk for bronchial carcinoma and mesothelioma. Chest 105:144–150.

Hourihane DOB, Lessof L, Richardson PC (1966): Hyaline and calcified pleural plaques as an index of exposure to asbestos. A study of radiological and pathological features of 100 cases with a consideration of epidemiology. BMJ 1:1069–1074.

Huncharek M (1992): Changing risk groups for malignant mesothelioma. Cancer 69:2704–2711.

Iwatsubo Y, Pairon JC, Archambault de Beaune C, Chamming’s S, Bignon J, Brochard P (1994): Pleural mesothelioma: A descriptive analysis based on a case-control study and mortality data in Ile de France, 1987–1990. Am J Ind Med 26:77–88.

Järvholm B, Sandén A (1986): Pleural plaques and respiratory function. Am J Ind Med 10:419–426.

Järvholm B, Arvidsson H, Bake B, Hillerdal G, Westrin CG (1986): Pleural plaques-asbestos-ill-health. Eur J Respir Dis 68(suppl 145):1–59.

Kilburn KH, Warshaw RH (1990): Abnormal pulmonary function associated with diaphragmatic pleural plaques due to exposure to asbestos. Br J Ind Med 47:611–614.

Kouris SP, Parker DL, Bender AP, Williams AN (1991): Effects of asbestos-related pleural disease on pulmonary function. Scand J Work Environ Health 17:179–183.

Lancet (Editorial) (1994): Research after death. Lancet 344:1517–1518.

Lee PN (1994): Comparison of autopsy, clinical and death certificate diagnosis with particular reference to lung cancer. A review of the published data. APMIS 102(suppl 45):3–42.

Leigh J, Hull B, Davidson P (1996): ‘‘The Incidence of Mesothelioma in Australia 1992 to 1994.’’ Sidney: Australian Mesothelioma Register.

Loomis DP, Collman GW, Rogan WJ (1989): Relationship of mortality, occupation, and pulmonary diffusing capacity to pleural tickening in the First National Health and Nutrition Examination Survey. Am J Ind Med 16:477–484.

Murai Y, Kitagawa M, Hiraoka T (1995): Asbestos body formation in the human lung: Distinctions by type and size. Arch Environ Health 50:19–25.

Peto J, Hodgson JT, Matthews FE, Jones JR (1995): Continuing increase in mesothelioma mortality in Britain. Lancet 345:535–539.

Schiffman MH, Pickle LW, Fontham E, Zahm SH, Falk R, Mele J, Correa P, Fraumeni JF Jr (1988): Case-control study of diet and mesothelioma in Louisiana. Cancer Res 48:2911–2915.

Sichletidis L, Daskalopoulou E, Chloros D, Vlachogiannis E, Vamvalis C (1992): Pleural plaques in a rural population in Central Macedonia, Greece. Med Lav 83:259–265.

Smith DD (1994): Plaques, cancer, and confusion. Chest 105:8–9.

Weiss W (1993): Asbestos-related pleural plaques and lung cancer. Chest 103:1854–1859.