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Latency periods in asbestos-related mesothelioma of the pleura

C Bianchi[1], L Giarelli[2], G Grandi[2], A Brollo[1], L Ramani[1], C Zuch[1]

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Latency periods (time intervals elapsing between first exposure to asbestos and death) were examined in 421 cases of malignant pleural mesothelioma, diagnosed in the Trieste–Monfalcone area, Italy. Occupational data were collected from the patients or from their relatives by personal or telephone interviews. Routine lung sections were examined for asbestos bodies in 370 cases. Latency periods, calculated in 312 cases, ranged from 14 to 72 years (mean 48.7, median 51). Latency periods differed significantly from one occupational group to another. Mean latency periods were 29.6 among insulators, 35.4 among dock workers, 43.7 in a heterogeneous group defined as various, 46.4 in non-shipbuilding industry workers, 49.4 in shipyard workers, 51.7 among women with a history of domestic exposure to asbestos, and 56.2 in people employed in maritime trades. The ANOVA test indicated a correlation between latency periods and occupational groups. Latency periods in people with asbestos bodies visible in routine lung sections did not differ from those seen in cases with no evidence of asbestos bodies. These data suggest that intensity of exposure is a relevant, but not the only, factor in determining the duration of latency periods.

Key words: Asbestos exposure, environmental cancer, latency periods, mesothelioma, pleura, shipbuilding industry.

Introduction

Latency periods in asbestos-related mesothelioma may be defined as the time intervals elapsing between the first exposure to asbestos and the time of death (or alternatively of the first symptoms, or of the diagnosis). Latency periods in asbestos-related mesothelioma show wide variations (Lanphear and Buncher, 1992).

Some findings suggest that the intensity of the exposure to asbestos does not completely explain the differences in latency periods (Bianchi *et al*, 1993b, 1994). To obtain more data on the mechanisms involved in latency periods, we analysed a large series of malignant pleural mesotheliomas, diagnosed in the Trieste–Monfalcone area.

Trieste–Monfalcone district is a narrow coastal strip, located in north-eastern Italy, on the border of Slovenia. In the past this area has been characterized by a high concentration of shipbuilding industries. A very high incidence of asbestos-related mesothelioma has been documented in Trieste (Giarelli *et al*, 1992, 1994), as well as in Monfalcone (Bianchi *et al*, 1993b).

Methods

A series of 421 malignant pleural mesotheliomas, diagnosed at Trieste University and at Monfalcone Hospital during 1968–96, were studied. Mesothelioma was diagnosed on, or confirmed by, necropsy findings in 374 cases. In a further 43 cases the pathological diagnosis was made on pleural biopsy specimens, and in the remaining four cases on cytological examination of the pleural fluid.

[1]*Laboratory of Pathological Anatomy, Hospital of Monfalcone, 34074 Monfalcone, Italy.* [2]*Institute of Pathological Anatomy, University of Trieste, Trieste, Italy. Correspondence to: C Bianchi. Fax: (+39) 481 487 677.*

Occupational histories were obtained from the patients themselves or from their relatives by personal or telephone interviews.

In 370 cases routine lung sections, generally obtained at necropsy and sometimes at surgery, were histologically examined for asbestos bodies.

The classification of a given case as asbestos-related was mainly based on the occupational data. However, in most of the cases, the existence of previous non-trivial exposure to asbestos was documented by objective signs (pleural plaques and/or lung asbestos bodies).

Statistical analysis was performed using Epi Info, version 5, from the Centers for Disease Control (Atlanta, Georgia). The ANOVA test was used to analyse the distribution of latency periods in the various occupational groups. Student's *t* test was used to compare mean latency periods among people with and without asbestos bodies in routine lung sections.

Results

Over 90% of the cases were classified as asbestos-related. However, precise chronological data about the first exposure to asbestos were obtained for 312 patients (292 men and 20 women, aged between 32 and 91 years). In such cases latency periods ranged from 14 to 72 years, most between 40 and 59 years (Figure 1). The different occupational groups showed substantial differences in latency periods (Figure 2). Insulators and dock workers generally had latency periods below 40 years. At the other extreme, the latency periods of women with histories of domestic exposure to asbestos (they had cleaned the work clothes of people occupationally exposed), and the latency periods of patients employed in maritime trades, were generally higher than 40 years. Intermediate values were observed in the remaining categories. The mean latency periodsw in the above occupational groups ranged from 29.6 to 56.2 years (Table 1).

The ANOVA test indicated a correlation between latency period and occupational groups ($P < 0.000001$).

Of 287 patients for whom both latency period data and routine lung sections were available, 198 (69%) showed asbestos bodies. The prevalence of positive findings varied largely from one category to another, ranging from 27% to 100% (Table 1). The latency periods in patients with asbestos bodies in routine lung sections are reported in Table 1. Mean latency period in people with asbestos bodies visible in

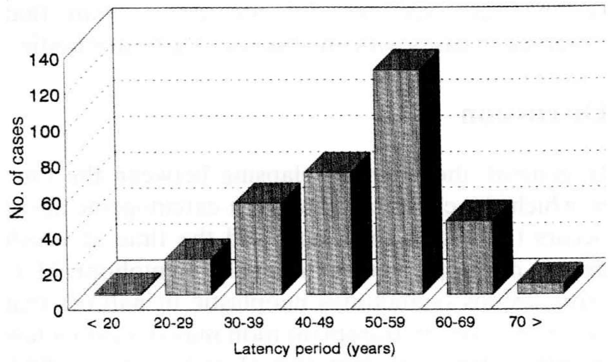

Figure 1. Latency periods in 312 cases of malignant pleural mesothelioma.

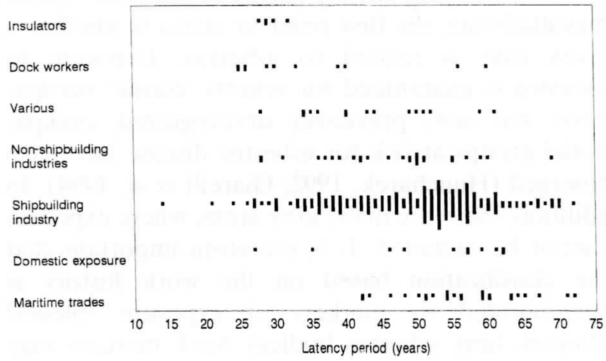

Figure 2. Latency periods by occupation in 312 cases of malignant pleural mesothelioma.

Table 1. Mean latency periods by occupation and presence of asbestos bodies in routine lung sections

Occupation	No of cases	Mean LP	Cases with AB (%)	Mean LP in the cases with AB
Insulators	5	29.6	80.0	30.0
Dock workers	11	35.4	100.0	35.4
Various	15	43.7	50.0	48.0
Non-shipbuilding industry	27	46.4	56.0	47.0
Shipbuilding industry	216	49.4	74.0	49.9
Domestic exposure	11	51.7	27.3	60.7
Maritime trades	27	56.2	52.2	56.0
Total	312	48.7	69.0	48.9

AB = Asbestos bodies
LP = Latency period

routine lung sections did not differ from that observed in cases with an absence of asbestos bodies.

Discussion

In general, the intervals elapsing between the time in which the exposure to a given carcinogenic agent occurs (or begins to occur), and the time at which cancer develops, vary extensively. Lymphoproliferative lesions (sometimes neoplastic in nature) that occur after organ transplantation may develop a few months after transplantation (London *et al*, 1995). At the other end of the spectrum, the development of mesothelioma may require incubation periods of 70 years. Intervals between some years and some decades are seen with radiogenic cancer (Mark *et al*, 1994; Nikiforov and Gnepp, 1994; Salvati *et al*, 1994).

When studying latency period in asbestos-related mesothelioma, the first point to assess is whether a given case is related to asbestos. Exposure to asbestos is guaranteed for several 'classic' occupations, but new, previously unrecognized, occupational groups at risk for asbestos disease have also emerged (Huncharek, 1992; Giarelli *et al*, 1994). In addition, there are many grey areas, where exposure cannot be excluded. It is therefore important that the classification based on the work history is corroborated by markers of exposure (pleural plaques, lung asbestos bodies). Such markers may also give reliable information about the intensity of the exposure (Bianchi *et al*, 1991).

As the workplace is the source of the exposure in most asbestos-related mesotheliomas, it is not generally difficult to determine the onset of the exposure. However, the first exposure may be difficult or impossible to establish exactly in the case of non-occupational exposure.

In previous studies on mesothelioma in the Trieste–Monfalcone area, latency periods were defined as time intervals between first exposure and death (Giarelli *et al*, 1992, 1994; Bianchi *et al*, 1994), and as time intervals between first exposure and diagnosis of the tumour (Bianchi *et al*, 1993b). In the present analysis the former definition was adopted, because in various cases, retrospectively examined, the time of the diagnosis (and/or of the first symptoms) could not be accurately determined.

The present data show that latency periods markedly differ among various occupational groups. The shortest mean latency periods were seen among insulators and dock workers. Insulation workers were by far the most heavily exposed to asbestos; in fact, they handled asbestos daily. Dock workers had been employed in the port of Trieste, where they frequently loaded and unloaded asbestos. Previous inquiries revealed that heavy pollution occurred in such workplaces (Giarelli *et al*, 1994). The severe degree of exposure to asbestos these people had, is also indicated by the very high prevalence of cases with asbestos bodies visible in routine lung tissue sections.

The longest mean latency periods were found among men employed in maritime trades and among women with domestic exposure to asbestos. Both these categories generally experience exposures of relatively low intensity, the amounts of lung asbestos bodies frequently being below 1,000 per gram of dried tissue, and more rarely of some thousands/gram (Bianchi *et al*, 1991).

The data for the most heavily exposed people as well as those for the groups with the lowest exposures are exactly the same as would be expected, if an inverse correlation exists between the intensity of exposure to asbestos and the duration of latency period. Obviously, this conclusion is weakened by the fact that in the present series some groups (notably the insulators) were small in number.

The findings on shipyard workers are not easy to explain in terms of a dose-effect correlation. It is true that within this category the degrees of exposures are scattered along a very wide spectrum. However, the intensity of exposure among shipyard workers is high, as indicated by the high prevalence of large pleural plaques (71.7%), the high prevalence of asbestos bodies in lung sections (42.8%) and by the numbers of asbestos bodies in lung tissue (frequently over 10,000/gram) (Bianchi *et al*, 1991). On the whole, exposure to asbestos among shipyard workers seems to be similar to that experienced by insulators rather than like that experienced by sailors. Therefore, the long latency period seen in a large proportion of shipyard workers is quite unexpected. The hypothesis that mesothelioma involves a sub-category of shipyard workers with relatively mild exposures (the most heavily exposed persons having pulmonary asbestosis and lung cancer) should be considered. However, the high percentage of shipyard workers with asbestos bodies, visible in routine lung sections (Table 1), indicates that these patients had had heavy exposures. Moreover, latency periods in shipyard workers with asbestos bodies in routine lung sections did not differ from latency periods among those without asbestos bodies. These data suggest that latency periods among shipyard workers do not depend on the intensity of exposure alone.

The type and amount of asbestos could help to determine the duration of the latency period. Investigations performed on pleura and lung tissues from people who had worked in the Monfalcone shipyards showed both amphibolic and chrysotilic fibres (Dodson *et al*, 1990). This clearly indicates that 'mixed' exposure occurred in the shipyards of this area. The remaining main categories of worker were also presumably exposed to various types of asbestos.

Another point to be considered is the possible association between latency period and smoking. Asbestos may induce both malignant mesothelioma and lung carcinoma, the latter in smokers. The smoking habits in a given population exposed to asbestos will influence the proportion of mesotheliomas and lung carcinomas. Smoking could also influence the latency periods in mesothelioma. For instance, being a non-smoker (or light smoker) might induce longer survival, and therefore could favour the development of mesothelioma after a long latency period. Investigation of pleural mesothelioma and lung carcinoma simultaneously would help resolve this. While previous findings (Bianchi *et al*, 1993a) suggest that in our area mesothelioma patients do not differ in their smoking habits from the general population, this topic requires further investigation.

The discussion about latency period is not of simply academic interest. Despite bans on (or limitations in) the use of asbestos, the incidence of malignant mesothelioma is increasing in various industrialized countries (Bégin *et al*, 1992; Facchini *et al*, 1993; Iwatsubo *et al*, 1994; Damhuis and Planteydt, 1995; De Vos Irvine, 1995; Peto *et al*, 1995; Leigh *et al*, 1996). In recent decades, the intensity of exposure has been reduced in many workplaces. However, more people have been exposed (for instance in the construction industry), and this indicates that a new wave of mesotheliomas is to be expected (Peto *et al*, 1995). On the other hand, the results obtained by various treatments for mesothelioma are not encouraging (de Pangher Manzini *et al*, 1993; Shin *et al*, 1995). In this context, how to prevent mesothelioma in healthy people previously exposed to asbestos becomes a major issue. If the factors responsible for the duration of latency period are identified, a way could be found to modify this duration. As the longest latency period in asbestos-related mesothelioma is very close to the mean duration of human life, the prolongation of the latency period could mean preventing the development of the tumour.

References

Bégin R, Gauthier JJ, Desmeules M, Ostiguy G (1992). Work-related mesothelioma in Quebec, 1967–1990. *Am J Industrial Med* **22:** 531–42.

Bianchi C, Brollo A, Ramani L, Bertè R (1991). Exposure to asbestos in Monfalcone, Italy. A necropsy-based study. In *Autopsy in Epidemiology and Medical Research* (eds Riboli E, Delendi M); IARC, Lyon, pp. 127–40.

Bianchi C, Brollo A, Ramani L, Zuch C (1993a). Asbestos exposure in pulmonary and pleural malignancies. A study of 307 cases. In *Proceedings of the Eighth International Conference on Occupational Lung Diseases* (eds Hurych J, Lesage M, David A); ILO, Geneva, pp. 335–40.

Bianchi C, Brollo A, Ramani L, Zuch C (1993b). Asbestos-related mesothelioma in Monfalcone, Italy. *Am J Industrial Med* **24:** 149–60.

Bianchi C, Giarelli L, Grandi G, Brollo A (1994). Malignant mesothelioma of the pleura. A survey of 357 cases. In *Proceedings of the XVI International Cancer Congress* (eds Rao RS, Deo MG, Sanghvi LD); Monduzzi, Bologna, pp. 1239–42.

Damhuis RAM, Planteydt HT (1995). Trends in incidence of pleural mesothelioma in the Rotterdam area. *Int J Cancer* **60:** 883.

de Pangher Manzini V, Brollo A, Franceschi S, De Matthaeis M, Talamini R, Bianchi C (1993). Prognostic factors of malignant mesothelioma of the pleura. *Cancer* **72:** 410–7.

De Vos Irvine H (1995). Mesothelioma. *Lancet* **345**: 1233.

Dodson RF, Williams MG Jr, Corn CI, Brollo A, Bianchi C (1990). Asbestos content of lung tissue, lymph nodes, and pleural plaques from former shipyard workers. *Am Rev Respir Dis* 142: 843–47.

Facchini U, Branzaglia P, Ludwig N, Riboldi L, Bertazzi PA (1993). Rischio amianto: uno studio sui certificati di morte per mesotelioma della pleura, anni 1969–1988. *Acta Oncologica* **14:** 221–31.

Giarelli L, Bianchi C, Grandi G (1992). Malignant mesothelioma of the pleura in Trieste, Italy. *Am J Industrial Med* **22:** 521–30.

Giarelli L, Bianchi C, Grandi G (1994). Asbestos-related mesothelioma of the pleura in Trieste, Italy. In *The Identification and Control of Environmental and Occupational Diseases* (eds Mehlman MA, Upton A); Princeton Scientific Publishing Co, Princeton, pp. 343–51.

Huncharek M (1992). Changing risk groups for malignant mesothelioma. *Cancer* **69:** 2704–11.

Iwatsubo Y, Pairon JC, Archambault de Beaune C, Chammings 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 Industrial Med* **26:** 77–88.

Lanphear BP, Buncher CR (1992). Latent period for malignant mesothelioma of occupational origin. *J Occupational Med* **34:** 718–21.

Leigh J, Hull B, Davidson P (1996). *The Incidence of Mesothelioma in Australia 1992 to 1994. Australian Mesothelioma Register Report, 1996.* Australian Mesothelioma Register, Sydney.

London NJ, Farmery SM, Will EJ, Davison AM, Lodge JPA (1995). Risk of neoplasia in renal transplant patient. *Lancet* **346:** 403–6.
Mark RJ, Poen J, Tran LM, Fu YS, Selch MT, Parker RG (1994). Postirradiation sarcomas. A single-institution study and review of the literature. *Cancer* **73:** 2653–62.
Nikiforov Y, Gnepp DR (1994). Pediatric thyroid cancer after the Chernobyl disaster. Pathomorphologic study of 84 cases (1991–92) from the Republic of Belarus. *Cancer* **74:** 748–66.
Peto J, Hodgson JT, Matthews FE, Jones JR (1995). Continuing increase in mesothelioma mortality in Britain. *Lancet* **345:** 535–9.
Salvati M, Puzzilli F, Bristot R, Cervoni L (1994). Post-radiation gliomas. *Tumori* **80:** 220–3.
Shin DM, Fossella FV, Umsawasdi T *et al* (1995). Prospective study of combination chemotherapy with cyclophosphamide, doxorubicin, and cisplatin for unresectable or metastatic malignant pleural mesothelioma. *Cancer* **76:** 2230–6.