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Incidence of Malignant Pleural Mesothelioma in Coastal and Continental Croatia: Epidemiological Study

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Aim. To evaluate the actual incidence of malignant pleural mesothelioma in Croatia, geographical distribution of the disease, and relevance of occupation and some other characteristics of diseased subjects.

Method. Data on the incidence of pleural mesothelioma over a seven-year period (1991-1997) were collected from the Croatian Cancer Registry. In each case, the tumor diagnosis was histologically verified. Registration of the patients was based on their place of residence. Also, in 2001, a short questionnaire was sent to patients' families to gather additional information on patients' occupation (exposure to asbestos), smoking habits, and length of residence in the registered place. In many cases some of the answers had to be clarified by telephone or through a personal contact. Data obtained from 20 counties (administrative units) of Croatia were grouped into two larger areas: coastal and continental. The data for the city of Zagreb were presented separately.

Results. During the 1991-1997 period, the Registry recorded a total of 248 malignant pleural mesotheliomas (197 in men and 51 in women). The poll gathered additional data for 194 patients (78.2%): 153 (77.7%) men and 41 (80.4%) women. Eight in a million people on average were diagnosed with malignant pleural mesothelioma per year. Age standardized incidence rates (per 100,000) by residence showed an uneven geographical distribution for men: 2.66 in coastal area, 0.69 in continental area, and 0.75 in the city of Zagreb. Goodness-of-fit test for observed rates vs expected for Croatia were chi-square = 145, df = 2, $p<0.001$; post-hoc tests: coastal vs continental area chi-square = 12.3, df = 1, $p = 0.001$; and coastal area vs city of Zagreb chi-square = 4.4, df = 1, $p = 0.035$. In women with mesothelioma, these rates were 0.38, 0.24, and 0.18, respectively, and the differences were not statistically significant.

Conclusion. Assuming that the information obtained by the poll on the occupation of diseased subjects was a true characterization of all recorded cases of pleural mesothelioma, more than two-thirds of subjects with the studied tumor had an occupational exposure to asbestos. Uneven distribution of the tumor, with higher rate in men in the coastal area, may be related to shipbuilding and other industrial sources of asbestos exposure in that part of the country.

Keywords: *asbestos; carcinogens; Croatia; environmental exposure; environmental health; mesothelioma; occupational health*

Malignant mesothelioma is a relatively rare tumor. Its basic annual incidence is around one case per million and it is age-dependent (1). The incidence of malignant pleural mesothelioma is about three times higher in men than in women. The link between malignant mesothelioma and asbestos exposure was first suggested by Wagner et al (2) in 1960, in a study of diffuse pleural mesothelioma associated with asbestos mining in South Africa. Subsequent studies have found consistently elevated rates of mesotheliomas in workers exposed to asbestos (3-8). Pleural mesotheliomas are much more common than peritoneal mesotheliomas and account for about 90% of mesothelioma cases (9). Studies demonstrate a latency period of 30-35 years from the first exposure to the onset of the disease (3). Although higher cumulative exposure to asbestos generally correlates with the increased risk of malignant mesothelioma, studies have revealed that the tumor may develop from short-term exposure (1 to 2 years) and lower exposure levels. Non-occupational exposure to asbestos has also been incriminated. Household contacts with asbestos-contaminated clothes are also a recognized risk (9).

Asbestos fiber type influences the incidence of malignant mesothelioma. Although all fiber types appear capable of inducing the tumor, rates are lower in exposure to chrysotile alone. Smoking does not seem to increase the risk of mesothelioma (9,10).

Clusters of malignant mesotheliomas, generally asbestos-related, have been reported in various small areas in Europe since 1960, frequently involving districts with shipbuilding activities (1,11). A particularly dramatic increase in the incidence of mesothelioma was noted in European countries during the 1980s (5-8,12,13). At present, the annual numbers of malignant mesothelioma cases in many European countries

Table 1. Malignant pleural mesothelioma in Croatia in 1991-1997: recorded cases (R) and cases with questionnaire data (Q)[a]

	1991		1992		1993		1994		1995		1996		1997		Total	
Subjects	R	Q	R	Q	R	Q	R	Q	R	Q	R	Q	R	Q	R	Q
Men	17	14 (82)	18	12 (67)	28	21(75)	28	24 (86)	28	21 (75)	40	29 (73)	38	32 (84)	197	153 (78)
Women	3	3 (100)	5	5 (100)	9	8 (89)	6	5 (83)	15	10 (67)	8	6 (75)	5	4 (80)	51	41 (80)
Total	20	17 (85)	23	17 (80)	37	29 (78)	34	29 (85)	43	31 (72)	48	35 (73)	43	36 (83)	248	194 (78)

[a]Numbers in parenthseses indicate response rate (%) to the questionnaire.

Table 2. Recorded cases of malignant pleural mesothelioma in Croatia in the 1991-1997 period by years and patients' place of residence

			No. of patients recorded per year								
Area		No. of inhabitants[a]	1991	1992	1993	1994	1995	1996	1997	Total	Rate[b]
Coastal:	men	775,838	13	10	15	20	19	31	22	130	2.4
	women	804,375	2	4	2	2	7	2	3	22	0.4
	total	1,580,213	15	14	17	22	26	33	25	152	1.4
Continental:	men	1,176,495	3	6	9	7	8	5	10	48	0.6
	women	1,249,731	0	1	4	4	6	6	2	23	0.3
	total	2,426,226	3	7	13	11	14	11	12	71	0.4
City of Zagreb:	men	366,290	1	2	4	1	1	4	6	19	0.7
	women	411,536	1	0	3	0	2	0	0	6	0.2
	total	777,824	2	2	7	1	3	4	6	25	0.5

[a]The figures are based on the 1991 census.
[b]Rate per 100,000 inhabitants.

are several times higher than those normally expected. Recent studies report on the incidence of malignant mesothelioma in Central and Eastern Europe (14,15). In some specific areas, such as central Turkey, clusters of environmental mesothelioma induced by asbestos or related fibers (erionite) have been reported (16,17).

Croatia has some specific sources of exposure to asbestos, such as shipyards, asbestos-cement industry, and asbestos processing. The aim of this study was to evaluate the actual malignant mesothelioma incidence in the country, its geographical distribution, and occupations of the patients. Only the cases of malignant pleural mesothelioma were analyzed.

Method

The study was performed in 2001. Data on the incidence of malignant pleural mesothelioma (code number 163 by the International Classification of Diseases – 9th Revision) in the whole Croatia over the seven-year period, 1991-1997, were collected retrospectively from the Croatian Cancer Registry. The diagnosis of the tumor in each recorded case was histologically verified. Its histological confirmation, although rather difficult and sometimes inaccurate (18), is a prerequisite for the inclusion of tumor under this particular diagnosis in the Registry. The patients with mesothelioma were registered according to their place of residence.

To gather additional information on the patients' occupation (possible exposure to asbestos), smoking habits, and length of residence in the registered place, a short questionnaire was sent to their families in 2001. If the answers had to be clarified, the family was contacted by phone or in person.

Analysis of the tumor rates was made according to age, sex, and permanent residence of the patients. Data obtained from 20 counties in Croatia were grouped into two larger areas: coastal and continental. Data for the city of Zagreb were presented separately. As there was no significant change in the population structure during the studied period, calculation of the rates was based on the 1991 population census, when Croatia had 4,784,265 inhabitants (2,318,623 men and 2,465,642 women). For the evaluation of geographical differences in tumor rates, age standardization was done with the direct method (19). Regional heterogeneity in standardized incidence rates was evaluated by chi-square test for goodness-of-fit between the observed regional rates and the expected rate for the whole Croatia for the same time period; $p<0.05$ was considered to be significant.

Table 3. Recorded cases with malignant pleural mesothelioma by age, sex, and residence

Areas	≤44	45-54	55-64	65-74	≥75	Total
Coastal:						
men	9	33	51	27	10	130
women	0	5	9	7	1	22
total	9	38	60	34	11	152
Continental:						
men	7	8	14	11	8	48
women	1	3	8	7	4	23
total	8	11	22	18	12	71
City of Zagreb:						
men	1	4	7	5	2	19
women	1	0	2	2	1	6
total	2	4	9	7	3	25
Total:						
men	17	45	72	43	20	197
women	2	8	19	16	6	51
total	19	53	91	59	26	248

Results

The Croatian Cancer Registry recorded a total of 248 malignant pleural mesotheliomas between 1991 and 1997 (197 men and 51 women). The questionnaire data were available for 194 patients: 153 men and 41 women, with 77.7% and 80.4% response rate, respectively (Table 1). The recorded incidence fluctuated with time, but the trend was clearly increasing over the years.

The tumor incidence for the 1991-1997 period was 0.8 per 100,000. It was higher in men than in women (1.2 vs 0.3 per 100,000, respectively). The tumor rate for men was the highest in the coastal area (Table 2). The rates for women did not differ across geographical regions.

We analyzed distribution of patients with pleural mesothelioma by age, sex, and residence (Table 3). Out of the total number of patients, 7.7% were younger than 44 years of age, and 10.5% were 75 or older. The majority of the patients (60.5%) were in the age group 65-74. The youngest patient was a 35-year-old man. Based on the questionnaire data, he had a his-

Table 4. Occupation of patients with pleural mesothelioma, according to the questionnaire data[a]

Area		No. of patients in shipbuilding industry	asbestos cement production	other[b]	construction industry	agriculture	other[c]
Coastal:	men	54	12	9	18	2	10
	women	2	0	6	0	1	12
	total	56	12	15	18	3	22
Continental:	men	0	0	12	7	6	9
	women	0	0	2	0	9	5
	total	0	0	14	7	15	14
City of Zagreb:	men	0	0	8	3	0	3
	women	0	0	0	0	0	4
	total	0	0	8	3	0	7

[a]Questionnaires were sent to the patients' families in 2001. Response rate was 78.2%.
[b]Activities involving exposure to asbestos: insulation workers (n = 5), asbestos processing (n = 8), asbestos textile workers (n = 6), transportation and storage of asbestos (n = 6), maintenance and repair of machines and items containing asbestos (n = 4), history of work in asbestos processing plants abroad (n = 4), naval machinists (n = 3), asbestos-cement worker's wife (n = 1).
[c]Blue collar workers (n = 9), technicians (n = 2), administrative staff (n = 10), persons with university education (n = 4), miscellaneous (n = 4), housewives (n = 14).

Table 5. Age-standardized incidence rates of malignant pleural mesothelioma by residence and sex of the patients in Croatia in the 1991-1997 period

Area	Rates/100,000[a]
Coastal:	
men	2.66
women	0.38
total	1.43
Continental:	
men	0.69
women	0.24
total	0.43
City of Zagreb:	
men	0.75
women	0.18
total	0.42
Total:	
men	1.34
women	0.27
total	0.74

[a]Goodness-of-fit test for observed rates vs expected rate for Croatia for men $p < 0.001$, chi-square = 14.5, df = 2. Post-hoc tests: coastal vs continental $p = 0.001$, chi-square = 12.3, df = 1; coastal vs city of Zagreb $p = 0.035$, chi-square = 4.4, df = 1; continental vs city of Zagreb $p = 0.905$, chi-square = 0.0, df = 1. No statistically significant differences among women from different areas.

tory of occupational exposure in an asbestos processing plant in another country. Another younger patient, a 38-year-old man, had been engaged in the machine maintenance on ships. All save two patients from the 44 or less age group had a history of occupational exposure to asbestos: 3 patients were shipbuilding workers, 3 worked in asbestos-cement industry, 4 were insulation and asbestos textile workers, and 3 were construction workers (Table 4).

There was no difference in the percentage of polled mesothelioma cases vs recorded cases by age, sex, and area of residence (data not shown).

Comparison of Croatian areas based on age-standardized incidence rates showed a significant difference in the incidence of the tumor in men between the coastal and two other areas (Table 5). In women, there was no significant difference in tumor rates between the areas.

Answers to the questionnaire used in the poll method revealed that 115 men suffering from malignant pleural mesothelioma were smokers. The highest percentage of smokers among patients was found in the continental area (86.2%), followed by the coastal area (72.6%) and the city of Zagreb (68.4%). The duration of smoking also differed by place of residence: 65% of men from the coast, 51.9% from the continent, and 43% from the city of Zagreb smoked for over 30 years. Women smoked much less (14.6%) and the duration of smoking did not differ by place of residence.

As far as place of residence was concerned, most patients (95%) had lived at the same location or even in the same house or apartment for many years.

Discussion

Our analysis of the data from 1991-1997 period showed that, on average, eight out of every million of people in Croatia were diagnosed with malignant pleural mesothelioma each year. Taking the rate of one case per million as expected under conditions without any specific exposure to agents that may contribute to the occurrence of tumor, the observed crude rate was approximately 8 times higher than predicted (1). As could be expected, the incidence of mesothelioma was age-dependent. Distribution of tumor cases in men vs women showed a 4:1 ratio. More than 60% of the total number of recorded cases of pleural mesothelioma were from the coastal area. Such distribution of malignant pleural mesothelioma was somewhat expected, considering the shipbuilding yards in Pula, Rijeka, Kraljevica, Šibenik, Trogir, Split, and Korčula; asbestos-cement industry in Vranjic-Split; and asbestos processing in Ploče (Fig. 1). There are no asbestos mines or areas with environmental endemic mesothelioma in Croatia, such as those described in the literature (16). Assuming that the information obtained by the poll is a true characterization of all recorded cases of pleural mesothelioma, it seems that more than two-thirds of people with the tumor had a verified occupational exposure to asbestos (shipyards activities, asbestos-cement production, and other industries involving asbestos exposure) or were presumably exposed to asbestos (construction workers). Malignant mesotheliomas of the pleura, which may occur spontaneously, are presumed to result from exposure to asbestos fibers if there is a credible history of asbestos exposure and reasonable latency period. Although data shown in Table 4 are only qualitative, most industrial activities on the list are undoubtedly connected with continuous or at least sporadic exposure to asbestos. This also

Figure 1. Sources of occupational asbestos exposure in Croatia. S – shipyards, C – asbestos/cement industry, P – asbestos/processing plant.

relates to construction industry due to the increased use of asbestos-based construction material. In case of housewives, the household contact with asbestos could be incriminated in only one of them (asbestos-contaminated clothes of her husband who used to work in the asbestos/cement plant).

The remaining third of the patients with pleural mesothelioma, whose occupation was not related to the asbestos exposure, still had the tumor incidence about two per million per year. An explanation of this finding could lie in non-occupational exposure to asbestos. Our previous studies indicated the importance of asbestos emissions in the environment around asbestos processing and asbestos-cement plants for the development of lung tumors, including pleural mesothelioma (20,21). Environmental exposure to asbestos may also be involved in enhancing the risk of respiratory tract tumors, particularly in jobs involving outdoor work (agriculture, construction) in areas contaminated by asbestos emitted from industrial sources. The importance of working outdoors in an area possibly contaminated by asbestos fibers has to be taken into consideration. As found in our previous study, out of the total number of people with respiratory tract tumors, 78% had a job that included working outdoors (20). Housewives involved in farming or gardening, which is rather common in the areas with asbestos processing and asbestos-cement plants, were also among them.

As far as smoking is concerned, based on the information obtained from the patients' families, the number of active smokers among men with mesothelioma was rather high (75.2%). From a questionnaire study carried out in 1972 among a sample of Croatian population aged between 38 and 57 years, 52% of men and 15% of women were regular smokers (22). In men smokers, about 20% smoked more than 20 cigarettes per day. Another study from 1974 involving a large representative sample of households in Croatia showed a prevalence of 57.6% smokers among men and 9.9% among women in the population aged 20-64 years (23). Higher percentage of active smokers among our subjects with mesothelioma does not necessarily entail the causal role of smoking in the occurrence of pleural mesothelioma, because relevant studies do not support the possibility that smoking could influence the development of this malignant tumor (9,10).

There were several limitations of our retrospective study. Data were collected from patients' families and could not be objectively verified. Assessment of exposure to asbestos and its effect was qualitative rather than quantitative, because a latency period before the manifestation of tumor can be very long. On the other hand, the tumor can also develop shortly after exposure. The second point to consider is the problematic diagnosis of mesothelioma. Even when histological examination is performed, serious difficulties may be encountered in both separating the primary and the secondary tumor, and distinguishing benign mesothelial proliferations from the malignant ones (15,18).

In spite of these limitations, the study clearly showed higher incidence of tumor diagnosed as malignant pleural mesothelioma over the seven-year period. Also, more than two-thirds of the recorded cases could be attributed to occupational exposure to asbestos. The uneven distribution of the tumor, with the higher rate in men in the coastal area, is obviously connected with shipbuilding and other industrial sources of asbestos located in that part of the country.

In Croatia, asbestos has not been banned yet. All asbestos used in the country (at present, about 4.000 tons/year) is imported. Maximal allowable concentration in the work environment is limited to 0.1 fiber/cm^3 for the tremolite asbestos, 0.2 fiber/cm^3 for crocidolite and anthophyllite, 0.5 fiber/cm^3 for amosite, and 2 fibers/cm^3 for actinolite and chrysotile asbestos (24). Although there have been efforts to substitute asbestos in shipyards with other materials and to avoid crocidolite asbestos in asbestos-cement and asbestos processing industry in the last 15-20 years, we can expect a higher incidence of malignant pleural mesothelioma for at least the next two decades due to the long latency period of this asbestos-related tumor.

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The incidence of malignant pleural mesothelioma in males in the UK is 3.4 per 100,000. There are around 2,700 new cases in the UK each year[3]. The incidence has increased slightly in the last decade[4].Â Malignant pleural mesothelioma has an increasing incidence in industrialised countries because of the previous widespread exposure to asbestos fibres and to the long lag period from time of exposure and the diagnosis of the disease[5]. The latent period between exposure and development of the tumour may be up to 50 years[4]. The number of deaths from mesothelioma in the UK rose from 153 in 1968 to around 2,400 people in 2012[3]. The incidence of mesothelioma is expected to peak at around 2020 and then to decline rapidly. Incidence of malignant pleural mesothelioma in coastal and continental Croatia: Epidemiological study. Article. Aug 2002.Â To evaluate the actual incidence of malignant pleural mesothelioma in Croatia, geographical distribution of the disease, and relevance of occupation and some other characteristics of diseased subjects. Data on the incidence of pleural mesothelioma over a seven-year period (1991-1997) were collected from the Croatian Cancer Registry. Aim: To evaluate the actual incidence of malignant pleural mesothelioma in Croatia, geographical distribution of the disease, and relevance of occupation and some other characteristics of diseased subjects. Method: Data on the incidence of pleural mesothelioma over a seven-year period (1991-1997) were collected from the Croatian Cancer Registry. In each case, the tumor diagnosis was histologically verified.Â Data obtained from 20 counties (administrative units) of Croatia were grouped into two larger areas: coastal and continental. The data for the city of Zagreb were presented separately. Results: During the 1991-1997 period, the Registry recorded a total of 248 malignant pleural mesotheliomas (197 in men and 51 in women). The predominant cause of malignant mesothelioma is inhalational exposure to asbestos, with approximately 70 percent of cases of pleural mesothelioma being associated with documented asbestos exposure. This topic will discuss the epidemiology and risk factors of pleural mesothelioma. â—The pathology, clinical presentation, evaluation, and staging, and treatment of malignant pleural mesothelioma are discussed separately.Â The annual incidence of mesothelioma in the United States is estimated to be approximately 3300 cases per year [1]. The incidence of mesothelioma in the United States peaked around the year 2000 and is now declining, secondary to control of exposure to asbestos [2]. Malignant pleural mesothelioma (MPM), the most common type, is the only mesothelioma that has a formal staging system. These mesotheliomas start in the pleura, which includes the lining of the lungs and the inner lining of the chest wall. The staging system most often used for MPM is the American Joint Committee on Cancer (AJCC) TNM system, which is based on 3 key pieces of information: The extent (size) of the main tumor (T): How far has cancer spread in the pleura?