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Malignant and Non-Malignant Asbestos-Related Pleural and Lung Disease: 10-Year Follow-Up Study

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Aim. To examine the presence of radiologically visible lung and pleural changes in patients who were exposed to the asbestos dust, and to correlate the progression of these changes with the duration and intensity of exposure and smoking. We also evaluated possible correlation between non-malignant asbestos-related pleural abnormalities and the occurrence of malignant pleural mesothelioma.

Methods. Among 7,300 patients who visited our department between 1991 and 2000 due to non-specific respiratory symptoms, we selected 2,420 with chest X-rays indicating the possible existence of non-malignant asbestos-related diseases. The selected group was followed-up for progression of radiological changes and the development of malignant pleural mesothelioma, and the changes were correlated with the intensity and duration of exposure to asbestos dust and smoking.

Results. Radiological changes characteristic for non-malignant asbestos-related pleural disease or lung asbestosis were identified in 340 (14%) out of 2,420 examined patients, of whom 77 (22.6%) developed malignant pleural mesothelioma, as compared with 13 patients out of 2,080 (0.6%) without radiological signs of asbestosis or pleural changes. Twenty-three (29.9%) patients who presented with a progression of pleural disease and lung asbestosis had a very significant incidence of malignant pleural mesothelioma ($p < 0.001$). We also found that 55 (71.4%) patients with the highest asbestos exposure level (grade 3) developed malignant pleural mesothelioma more often ($p = 0.044$). No correlation was found between malignant pleural mesothelioma development and duration of asbestos exposure ($p = 0.149$) or smoking habit ($p = 0.617$). Professionally exposed patients were at 3.3-times higher relative risk (95% confidence interval, 2.28-4.75) than those who were not exposed to develop malignant pleural mesothelioma.

Conclusions. The risk of developing lung asbestosis increased with the level of exposure to asbestos dust and smoking. The risk of developing pleural disease correlated with the intensity and duration of exposure, but not with smoking. The patients with progressive pleural and parenchymal changes are at particularly high risk of developing malignant pleural mesothelioma and must be under special surveillance.

Key words: *asbestos; asbestosis; Croatia; environmental exposure; mesothelioma; occupational exposure*

Malignant pleural mesothelioma belongs to the group of diseases that may be associated with asbestos exposure. It is widely accepted that malignant pleural mesothelioma can develop 40-50 years after the first exposure to higher concentrations of the asbestos dust, even if the exposure was very short (1-3). Based on some studies, there is a fear that the incidence of this disease will continue to increase, at least in the regions where great amounts of asbestos were used between 1950 and 1980 and means of protection were poor (4). These predictions are more relevant for rapidly urbanized and industrialized regions, with extremely intensified traffic. The expected annual incidence of malignant pleural mesothelioma amounts to 1.0-1.2 per 100,000 population, including professionally exposed individuals (5).

In Croatia, the expected age-standardized annual incidence of mesothelioma for the 1990-1997 period was 0.74 per 100,000 population: 0.43 per 100,000 population in the continental regions and 1.43 per 100,000 population in the littoral regions (from Istria to Dubrovnik) (6).

We determined the presence of radiologically visible lung and pleural changes in patients who had been exposed to the asbestos dust, and also correlated the progression of these changes with the duration and intensity of asbestos exposure and smoking.

Special attention was paid to the evaluation of possible correlation between non-malignant asbestos-related pleural abnormalities and malignant pleural mesothelioma.

Patients and Methods

Patients

We followed up a cohort of 7,300 patients with respiratory symptoms who visited the Department of Pulmonary Diseases, Split University Hospital, between January 1, 1991, and December 31, 2000. All patients came from the Split-Dalmatian County and Dubrovnik-Neretva County. The symptoms were either indicative of respiratory diseases caused by asbestos exposure or an indication of asbestos-related disease had already existed in their medical history. About two-thirds of these patients (n = 4,880) had respiratory complaints and symptoms that could not be related to the exposure to asbestos, whereas the remaining 2,420 patients had symptoms that could be related to asbestos (exposure at place of work or residence). All patients underwent diagnostic procedures, including X-ray examination interpreted according to the International Labor Office Classification of Radiographs of Pneumoconiosis from 1980 (7). Also, each patient filled out a standard questionnaire prepared by the Committee on the Etiology of Chronic Bronchitis; the questionnaire included the questions on the professional exposure to the asbestos dust (8). Written informed consent was obtained from all patients before inclusion in the study. The differential diagnosis excluded pleural disease or lung asbestosis in 2,080 (85.9%) patients, leaving 340 (14.0%) patients with confirmed pleural disease and lung asbestosis. Every year in the 1991-2000 period, 2,420 patients with symptoms that could be related to asbestos were called for an X-ray check up (Fig. 1). Each patient had at least three chest X-rays during the study period. We excluded the possibility of the existence of some other pulmonary diseases on the basis of physical examination; hematological, biochemical, and immunology laboratory analyses; pulmonary function tests; and bronchoscopy.

Assessment of Exposure to Asbestos Dust

We assumed that workers whose jobs were associated with the production of the asbestos dust or products containing asbestos were occupationally exposed; the exposure levels carried a small to great risk.

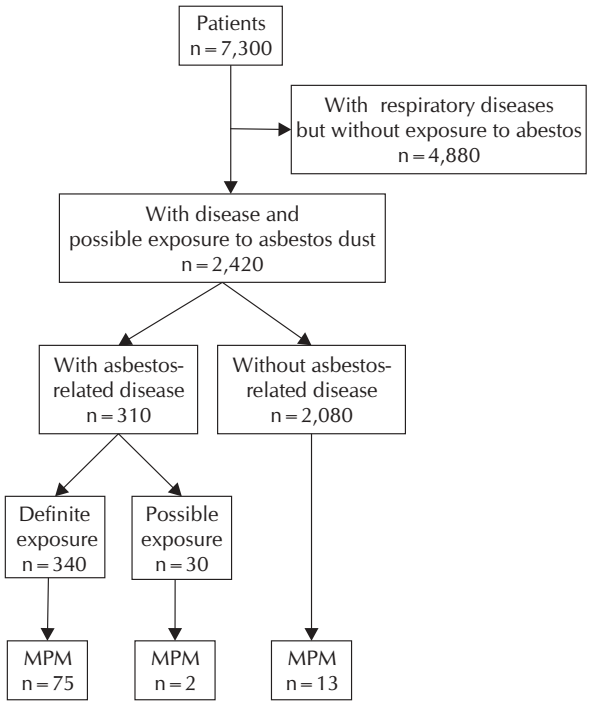

Figure 1. Flow-chart of patients in the study. MPM – malignant pleural mesothelioma.

Considering that the measurement of the asbestos dust concentration has never been done in the Split-Dalmatian County, where all workers came from, we classified our patients according to the type of their job, distance between their place of residence and occupational sources of the asbestos dust, or distance from large roads, and occupational exposure of some member of the family.

We estimated the jobs where a worker could be exposed to low concentrations of the asbestos dust as the level of a low risk (exposure grade 1). These included watchmen and indoor workers, such as staff in administrative buildings or factory restaurants occasionally visited by workers directly exposed to the asbestos dust (shipyards and industry of asbestos-cement or asbestos-textile and friction products) (1). Jobs at which a worker could be exposed to the allowed concentrations of the asbestos dust or where concentrations occasionally exceeded allowed limits for a working ambient were considered as the level of the intermediate risk (exposure grade 2). These included the jobs in asbestos-cement production, storage and transport of asbestos, maintenance of machinery in asbestos-cement and asbestos-textile industry, friction products industry, and shipyard jobs (outside of the body of the ship) (1). In the zone of high risk (exposure grade 3) were jobs at which workers could be exposed to concentrations of asbestos dust twofold or greater than allowed, including workers preparing asbestos-cement masses and finishing asbestos-cement products, preparing asbestos-textile mixtures, finishing friction products, and all shipyard jobs outside the body of the ship in the areas sprayed with asbestos mixtures. At present, only a few specific jobs inside the engine-room in the shipyard are at this risk level (1).

Nonoccupationally exposed patients were those living in the vicinity of sources of asbestos dust (low-to-moderate risk level); in the same household as workers with occupational exposure to asbestos (low-to-great risk level); in the regions far away from the sources of asbestos dust and not living with workers with occupational exposure to asbestos, but living in heavily populated and urbanized regions, or regions with heavy traffic (low-to-moderate risk level).

Smoking

According to their reported smoking habit, patients were classified into one of the following three categories: current smoker, former smoker, and never-smoker. Individuals who were smokers at the time of the interview and had been smoking regularly for at least a year were classified as current smokers. Individuals who reported they had been smoking regularly for at least a year but had stopped were classified as former smokers, and individuals who had not been smoking regularly for at least one year were classified as never-smokers.

Radiological Findings

Chest X-rays were evaluated according to the ILO 1980 Classification of Radiographs of Pneumoconiosis (7), and included an additional high-resolution computerized tomography (HRCT) of the lungs (9) whenever the radiologist thought it necessary. The final radiological report was always presented on the original ILO 1980 form, irrespective of the number or type of radiographs. The smallest radiological findings was a sign of asbestos-related lung disease with the characteristics of subcategory 1/0 s/s (increased profusion of small irregular opacities up to 1.5 mm in diameter, according to respective standards). Pleural radiological changes implied a sign of asbestos-related disease that had to show at least the characteristics of 1b classification category of pleural thickening (the width of circumscribed and/or diffuse thickening greater than 5 mm, and total length amounting to one-fourth of the projection of the lateral chest wall) with or without calcifications. If the pulmologist could not confirm the existence of any other disease that could account for specific radiological changes, he or she was authorized to diagnose pleural disease or lung asbestosis.

We established the progression of the disease if the profusion doubled (for example from 1/0 to 1/2). Any increase in comparison with previous findings was considered a progression of pleural changes. Malignant pleural mesothelioma was confirmed only after histological and immunohistochemical analysis of the material obtained during thoracoscopy and/or thoracotomy.

Follow-up

The inhabitants of the two southern Croatian counties gravitate mostly to our Department, including the majority of the patients with pleural disease, lung asbestosis, and malignant pleural mesothelioma. The patients who did not come for a regular checkup by the end of the study were contacted after the evaluation of data; two patients died in the meantime and their death certificates were obtained. We followed up the dynamics of progression of radiological changes, which are characteristic for pleural disease and lung asbestosis, and the occurrence of malignant pleural mesothelioma in groups with and without asbestos-related disease.

Statistics

Statistical analysis was done by using EPI-INFO 6.6 program (10). We used descriptive statistics, the median test, t-test for independent samples, and chi-square test with Yates correction with level of significance set at <0.05, and Kruskal-Wallis test. Relative risk for developing malignant pleural mesothelioma was also calculated.

Results

Out of 340 (14.0%) patients with asbestos-related diseases in the group of 2,420 patients with possible exposure to the asbestos dust, 298 (87.6%) had the diagnosis of pleural disease, 18 (5.3%) had the diagnosis of lung asbestosis, and 24 (7.1%) had both pleural disease and lung asbestosis. Two thousand and eighty (85.9%) patients were disease-free (Fig. 1).

The examined group included 280 (82.3%) men and 60 (17.6%) women, and the annual distribution showed that in most cases (279, or 82%) asbestos-related disease had been diagnosed until 1997. After 1997, the number of newly diagnosed patients stabilized at 13-18 new cases per year (Fig. 2).

Three hundred and ten patients (91.1%) were occupationally exposed to asbestos (Table 1): 130 (38.2%) were employees in the industry of asbestos-cement products, 107 (31.5%) worked in the industry of asbestos-textile and friction products, and 73 (21.5%) worked in the shipbuilding industry. For the remaining 30 (8.8%) patients – firemen, storage workers, drivers, metal industry workers, farmers, a radio-technician, and homemakers – there was a possibility that they had been in contact with products containing asbestos. In the case of homemakers and farmers, there was also an additional possibility of the communal and environmental exposure. The occupational exposure was not always confirmed on the occasion of the first visit because patients sometimes did not know what materials they were working with, so we asked them to describe the nature of their jobs from the first day of employment. The median exposure time to the asbestos dust was 20 years, varying from 8 to 30 years.

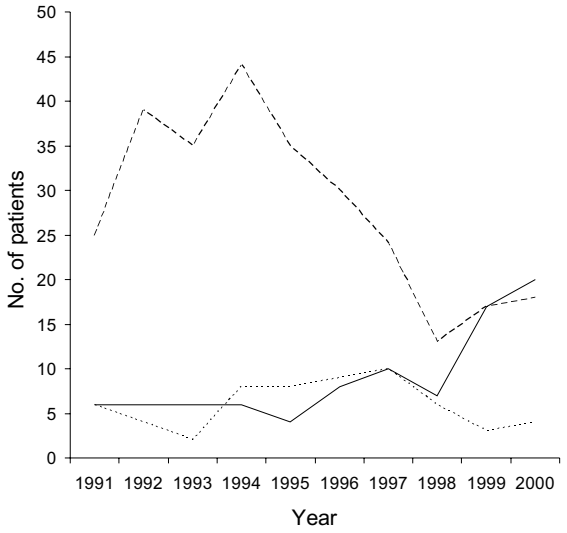

Figure 2. Number of patients with non-malignant asbestos related pleural diseases (PD), lung asbestosis (LA), PD + LA, or malignant pleural mesothelioma (MPM) in the Split University Hospital, 1991–2000. Full line – patients with MPM; dashed line – men with asbestosis; dotted line –

Out of 340 patients, 170 (50.0%) were smokers, 102 (30.0%) were former smokers, and 68 (20.0%) were never-smokers.

Radiological Changes

Forty-two patients (12.4%) had lung asbestosis grade 1 at the first radiographic examination, with ILO range of 1/0-1/2 ss and exposure grade 2 or 3. On the last checkup, we found 54 patients (16%) with the exposure grade 2 or 3 affected by lung asbestosis. A positive correlation was found between the progression of lung asbestosis and grade of exposure. Among 299 patients with exposure grade 2 or 3, 54 had the progression of lung asbestosis, whereas none of 39 patents with grade 1 exposure had such changes (chi-square = 7.09; df = 4; p = 0.008; Table 2).

No correlation was found between the progression of lung asbestosis and smoking habit. There were 30 smokers among 40 patients with a progression of lung asbestosis, 6 smokers among 14 with no progres-

Table 1. Occupational exposure to asbestos in patients (No, %) treated at the Split University Hospital, 1991-2000

	Exposure grade*				
Occupation	1	2	3	no data	Total
Asbestos-cement industry	9 (23.1)	50 (50.5)	71 (35.5)	0 (0)	130 (38.2)
Asbest-textil	1 (2.6)	38 (38.4)	47 (23.5)	0 (0)	86 (25.3)
Friction products	0 (0)	9 (9.1)	12 (6.0)	0 (0)	21 (6.2)
Shipyard	1 (2.6)	2 (2.0)	70 (35.0)	0 (0)	73 (21.5)
Firemen	4 (10.3)	0 (0)	0 (0)	0 (0)	4 (1.2)
Storage workers	6 (15.4)	0 (0)	0 (0)	0 (0)	6 (1.8)
Drivers	8 (20.5)	0 (0)	0 (0)	0 (0)	8 (2.4)
Metal industry	6 (15.4)	0 (0)	0 (0)	0 (0)	6 (1.8)
Radio-technician	1 (2.6)	0 (0)	0 (0)	0 (0)	1 (0.3)
Farmers	3 (7.7)	0 (0)	0 (0)	0 (0)	3 (0.9)
Homemakers (women)	0 (0)	0 (0)	0 (0)	2 (100.0)	2 (0.6)
Total	39 (100.0)	99 (100.0)	200 (100.0)	2 (100.0)	340 (100.0)

*According to Hillerdal (1).

Table 2. Grade of exposure to asbestos and development of lung asbestosis in 338 workers with occupational exposure to asbestos, 1991-2000

		No. (%) of workers			
		exposure grade*			
	Asbestosis grade† (range)	1	2	3	Total
First X-ray (ILO)†	1(0/- - 0/1)	39 (100.0)	76 (77.6)	181 (90.0)	296 (87.6)
	1(1/0 - 1/2ss)	0 (0)	22 (22.4)	20 (10.0)	42 (12.4)
	total	39 (100.0)	98 (100.0)	201 (100.0)	338 (100.0)
Last X-ray (ILO)	1(0/- - 0/1)	39 (100.0)	76 (77.6)	169 (84.1)	284 (84.0)
	1(1/0 - 1/2ss)	0 (0)	7 (7.1)	19 (9.5)	26 (7.7)
	2(2/1 - 2/3ss)	0 (0)	15 (15.3)	13 (6.5)	28 (8.3)
	total	39 (100.0)	98 (100.0)	201 (100.0)	338 (100.0)

*According to Hillerdal (1).
†According to ILO (7).

sion of lung asbestosis, and 134 (46.9%) among 286 who had negative examination results (chi-square = 11.69, df = 4, p = 0.19).

The duration of the exposure to the asbestos dust did not have any statistically significant influence on the progression of lung asbestosis: median exposure in patients with progression of lung asbestosis was 19.5 years, ranging from 15 to 27; median exposure in patients with no change was 19.5 years, ranging from 10 to 28 years; and median exposure in patients without disease was 20 years, ranging 8 to 30 years (Kruskal Wallis H = 0.589, df = 2, p = 0.74).

Pleural disease with or without calcifications was diagnosed in 322 (94.7%) patients on the first visit. During the 10-year follow-up, there was a statistically significant progression of pleural thickening (extending over 10 mm and/or more then one-fourth of chest wall), with or without calcifications, which occurred in workers with the highest grade of exposure (grade 3): 44 out of 58 (75.9%) patients had a progression of pleural disease vs 147 out of 260 (56.5%) patients who had no changes and 10 out of 20 (50%) who had negative examination results (chi-square = 16.48, df = 4, p = 0.002).

Exposure time also had statistically significant influence on the progression of pleural disease: median time since exposure was 20.5 years, ranging from 14 to 28 years, in patients with the progression of pleural disease; 20 years, ranging from 8 to 30 years, in the patients with no change; and 18 years, ranging between 8 and 28 years, in patients without disease (Kruskal Wallis H = 11.336, df = 2, p = 0.003).

Smoking did not have any statistically significant influence on the progression of pleural thickening, as showed by comparison of 16 patients out of 68 (23.5%) never-smokers vs 10 patients out of 102 (9.8%) former smokers vs 32 patients out of 170 (18.9%) smokers (chi-square = 9.40, df = 4, p = 0.051).

Malignant Pleural Mesothelioma

Among 2,420 patients with possible asbestos-related disease, we discovered 90 with malignant pleural mesothelioma, which were immunohistochemically verified on the specimens obtained by thoracoscopy and/or thoracotomy. Seventy-seven out of 340 (22.6%) patients had confirmed asbestos-related disease, whereas 13 out of 2,080 (0.6%) did not have it.

Out of 77 patients who developed malignant pleural mesothelioma, 54 (70.1%) already had pleural disease, 8 (10.4%) already had lung asbestosis, and 15 (19.5%) had both pleural disease and lung asbestosis. Thirteen out of 77 (0.6%) patients who developed malignant pleural mesothelioma had neither pleural disease nor lung asbestosis diagnosed before. Among 90 patients (82 men and 8 women) who developed malignant pleural mesothelioma, 35 (38.8%) were between 61 and 70 years of age (Table 3).

As the annual distribution of the patients with malignant pleural mesothelioma showed, in the period between 1991 and 1994, the average number of new cases with malignant pleural mesothelioma amounted to 6 (6.6%) cases per year (Fig. 2). In the period between 1994 and 2000, the number of newly diagnosed patients per year tended to increase, reaching the top number of 20 newly diagnosed patients in 2000.

As many as 40 (51.9%) patients developed malignant pleural mesothelioma 31-40 years after the first exposure to asbestos dust (Table 3).

Table 3. Patients with malignant pleural mesothelioma treated at the Split University Hospital and intervals from their first occupational asbestos exposure to diagnosis, 1991-2000

	No. (%) of patients	
Parameter (years)	men	women
Age at diagnosis:		
30-40	2 (2.4)	0 (0)
41-50	5 (6.1)	0 (0)
51-60	19 (23.2)	5 (62.5)
61-70	35 (42.7)	0 (0)
71-80	21 (25.6)	3 (37.5)
Total	82 (100.0)	8 (100.0)
Interval from the first occupational asbestos exposure to diagnosis:		
10-20	4 (5.6)	3 (50)
21-30	7 (9.9)	3 (50)
31-40	40 (56.3)	0 (0)
41-50	20 (28.2)	0 (0)
Total	71 (100.0)	6 (100.0)

The incidence of malignant pleural mesothelioma was significantly increased in patients with exposure grade 3, but did not correlate either with smoking habit or with exposure time (Table 4). However, patients with a progression of pleural disease and lung asbestosis during the follow-up had statistically significant increase in the incidence of malignant pleural mesothelioma (Table 4). Patients with professional exposure had a 3.29 times higher relative risk than those without professional exposure to develop malignant pleural mesothelioma (95% confidence interval, 2.28-4.75).

Table 4. Patients with malignant pleural mesothelioma (MPM) and non-malignant asbestos-related pleural diseases (circumscribed and/or diffuse bilateral pleural thickening with or without calcifications)*

Finding	No. (%) of patients			
	MPM present	MPM absent	chi-square	p
First visit X-ray:*				
PD	54 (70.1)	244 (92.8)	30.13	<0.001
LA	8 (10.4)	10 (3.8)		
PD + LA	15 (19.5)	9 (3.4)		
Last visit X-ray:				
PD	50 (64.9)	236 (89.7)	29.23	<0.001
LA	8 (10.4)	12 (4.6)		
PD + LA	19 (24.7)	15 (5.7)		
total	77 (100.0)	263 (100.0)		
Changes during follow-up:				
no change in PD	50 (64.9)	236 (89.7)	32.37	<0.001
no change in LA	4 (5.2)	10 (3.8)		
progression of PD + LA	23 (29.9)	17 (6.5)		
Smoking:				
never-smoker	13 (16.9)	55 (20.9)	0.96	0.617
former smoker	22 (28.6)	80 (30.4)		
smoker	42 (54.5)	128 (48.7)		
Exposure grade:				
grade 1	5 (6.5)	34 (13.0)	6.24	0.044
grade 2	17 (22.1)	81 (31.0)		
grade 3	55 (71.4)	146 (55.9)		
Duration of exposure (median, years)	20 (14-29)	20 (8-30)	2.075†	0.149

*PD –pleural diseases; LA – lung asbestosis.
†Kruskal-Wallis test.

Discussion

We found significant correlation between the intensity of exposure to the asbestos dust and both the progression of pleural disease and lung asbestosis and development of malignant pleural mesothelioma.

The patients included in this study live or work in the regions with some asbestos-related industry developed since 1950: the factory of asbestos-cement products, which is still active; the factory of asbestos-textile and friction products, which was closed in the early 1990's; and a few shipyards, where asbestos has not been used since the late 1980's. The late 1980's were the years of the biggest pollution of the working and living environment, because of the large production, poor protection at work, and unsatisfactory working hygiene (6). Furthermore, the whole region was rapidly urbanized and industrialized after the 1950's, and there was an increase in traffic. Therefore, the incidence of asbestos related diseases should be expected to grow, not only among individuals with occupational exposure but also among the members of their households and general population, especially among the population living in the vicinity of big factories that use asbestos. Unfortunately, measurements of the environmental concentration of asbestos fibers in the Split County have not been done yet. The measurements of the asbestos concentrations in the working environments have been correctly performed only in the asbestos-cement products factory, but not before 1990. The information that the factories of asbestos-cement products and shipyards have been using not only crysotile, but also crocidolite asbestos could be obtained only unofficially. Within the described context, it is obvious that it was not possible to estimate the cumulative exposure of our patients to asbestos fibers or to calculate occupational, communal, and/or household exposure. Therefore, we divided our patients into three groups by the grade of the exposure to the asbestos dust. The majority of the patients with pleural disease and lung asbestosis (82%) were identified until 1997, and the rest (18%) afterwards. The decrease in the asbestosis incidence is probably the result of socio-economical changes in the country, with many factories being closed down, less polluted environment, asbestos-free shipyards, and many workers laid off from work in the last 15 years.

Our results confirmed that small irregular lung opacities (ILO classification 1/0-1/2 ss) were mostly found in workers who were exposed to higher concentrations of the asbestos dust, ie, grade 2 and 3. We also have not found significant correlation between the progression of lung asbestosis and smoking habit. Some authors observed a clear association between smoking and small lung opacities, even after adjustment for occupational exposure to asbestos, age, and urbanization (1,11-13). Our results support the view that smoking may interfere with radiographic detection of early pneumoconiosis. According to our data, workers were mostly exposed to crysotile, and in the 1980's also to crocidolite. The duration of the exposure did not have significant influence on either the development or progression of lung asbestosis.

Most patients (94.7%) had pleural lesions already on their first visit to our Department. The lesions presented as diffuse or circumscribed bilateral pleural thickening with or without calcifications. Two hundred workers (58.8%) had grade 3 of exposure to asbestos concentrations. They worked at the preparation of asbestos-cement or asbestos-textile products and production of friction products, inside ships where they sprayed asbestos-containing insulating masses, as sheet metal workers, welders, carpenters, plumbers, and smiths. Many of them were employed during the period when crocidolite was used for insulation. The rest of the workers, who were exposed to smaller asbestos concentrations, grade 1 and 2, had less advanced pleural changes. The progression of

pleural disease of more than 10 mm and/or more than one-fourth of chest wall was documented in 58 (17%) patients. We confirmed the existence of correlation with the intensity of exposure and exposure time, but not with smoking habit.

It is well known that the exposure to high concentrations of the asbestos dust during many years causes pathological pleural changes, which can appear as diffuse and/or circumscribed pleural thickening with or without calcifications, as confirmed by the findings of asbestos bodies in the lung parenchyma (14,15). It was also confirmed elsewhere that the risk of developing pleural disease could show a twofold increase, with longer exposure time to the asbestos dust (16-18). Nevertheless, the incidence of pleural disease is not exclusively specific for asbestos exposure, and it can also be found in the population that have never had any occupational exposure (19,20), and more frequently among urban than among rural population (11). The same changes can appear in the population with household or close environmental exposure (21-23).

While the pleural disease and lung asbestosis incidence has been stagnating since 1997, the incidence in malignant pleural mesothelioma incidence has obviously been increasing. Our data show that during the 10-year follow-up the average annual incidence of malignant pleural mesothelioma amounted to 9 new patients per 600,000 population, including general population and those with occupational exposure. This translates to 1.53 cases of mesothelioma per 100,000 population. The predicted incidence of malignant pleural mesothelioma in some other European settings is 1.0-1.2 per 100,000, including the people with occupational exposure (5). Ćurin et al (6) reported an incidence of 1.43 per 100,000 in much larger part of the Croatian coast than that covered by our study. In northern Croatia, the incidence seems to be 0.43 per 100,000, which is even smaller. The majority of the patients with malignant pleural mesothelioma were occupationally exposed to the asbestos dust in shipbuilding industry, asbestos-cement, asbestos-textile, and friction products industry, indicating a high correlation between the presence of asbestos-related industry and the incidence of malignant pleural mesothelioma. Also, the incidence of malignant pleural mesothelioma was higher in patients who presented with the progression of pleural disease and lung asbestosis than in those who showed no progression of the disease during the follow-up.

More than two-thirds of the patients with malignant pleural mesothelioma were exposed to the highest concentrations of asbestos-dust (exposure grade 3), because they had been working at the preparation of asbestos-cement masses, asbestos-textile, in friction product industry, inside ships, and as joiners and plumbers. Only 5 (6.5%) patients with malignant pleural mesothelioma had grade 1 exposure. Our results showed statistically significant correlation between the incidence of malignant pleural mesothelioma and the exposure intensity, which is completely in accordance with other studies (1,4,24). We have not found the correlation with the length of exposure, or with smoking, which also corresponds to other studies (16,34).

Our results correspond to those published by Edge (24) who, as early as 1976, reported that the patients with pleural plaques were at much greater risk of developing malignant pleural mesothelioma, and to Hillardel's study (1) in which he calculated that the workers with pleural plaques were at 1.4-times greater risk of developing malignant pleural mesothelioma. There is also a difference in the risk of developing malignant pleural mesothelioma depending on the type of inhaled asbestos (crocidolyte and amosite increase the risk) (4,26,27) and the exposure intensity (4,16), but there is no correlation with smoking (16). It is important that a very short but intensive exposure can be significant for developing malignant pleural mesothelioma (2). Men are mostly affected, with men-to-women ratio of 8:1 (28), but it seems to be related with the type of profession and exposure intensity. Our group of patients with malignant pleural mesothelioma consisted mostly of men (91.1%) between 61 and 70 years of age. More than half of our patients were for first time occupationally exposed to the asbestos dust 31-40 years ago. Between the two time intervals, 1991-1993 and 1998-2000, the number of the patients with malignant pleural mesothelioma grew from 23.3% to 48.8%. The incidence of malignant pleural mesothelioma today is the result of the exposure that took place even 45-50 years ago (2-5,29,30). Our results confirmed this finding. Mortality of men born between 1945 and 1950 and affected by malignant pleural mesothelioma is expected to double in the next 20 years (31).

In the 1970's, crocidolite was the most common form of asbestos used in our country and its concentrations in working ambient usually exceeded maximum allowed limits. Usually, the concentration was measured in an inadequate way and transformation of different measuring units was not reliable (32). According to the World Health Organization recommendations, it was suggested not to use amphibole fibers (crocidolite, amosite, and tremolite) and to ban the use of their compounds (33). The International Agency for Research of Cancer (34) put all the types of asbestos in the first group of carcinogenic substances, marked as "can cause cancer". In our country, crocidolite has not been used since the 1980's, and only crysotile, which is supposed to be the less harmful, has been commercially used as asbestos. Nevertheless, there is no decrease in malignant pleural mesothelioma incidence, and crysotile that is contaminated with amphibole tremolite fibers seems to be responsible for that (35).

Some authors reported that 25-30% of malignant pleural mesothelioma could not be correlated to asbestos exposure (5). In our study, 14.5% of patients with malignant pleural mesothelioma, including two homemakers and three farmers, had no occupational exposure and most probably no contact with products containing asbestos. That shows that in our population the incidence of malignant pleural mesothelioma is mostly in correlation with occupational exposure to the asbestos dust. The fact that there are patients who

developed malignant pleural mesothelioma but did not have any contact with asbestos in the past, indicate that there may be some other etiological factor for the development of malignant pleural mesothelioma (36).

The limitation of this study was that we could not evaluate with absolute precision the grade of exposure of our patients to the asbestos dust, because measurements were done only occasionally and methods used were doubtful. Such measurements should be done systematically and the results would be of great importance not only for the evaluation of occupational but also of non-occupational exposure.

In conclusion, we may say that finding lung asbestosis and pleural disease on chest radiographs, and their progression, increase the risk of developing malignant pleural mesothelioma. Each person with lung asbestosis and pleural disease related to previous asbestos exposure has to be informed about its importance. The prohibition of the asbestos production can not solve the problem of asbestos-related disease and malignant pleural mesothelioma mortality, because it is related to the exposure that took place more than 20-50 years ago. It is very important to have a well-planned public health prevention program, especially in population living in regions with many occupational sources of asbestos, rapid urbanization, and heavy traffic.

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