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Increasing of Malignant Pleural Mesothelioma: Burning Issue in Split-Dalmatian County, Croatia

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A B S T R A C T

Asbestos-related diseases are one of the burning public health issues worldwide. The incidence and the epidemiological patterns of malignant pleural mesothelioma in Split-Dalmatian County, where a large part of Croatian industry related to asbestos processing and use have been situated were assessed in this study. The history of asbestos-related issues and development of current legislation in Croatia was also discussed briefly. Data on the incidence were collected retrospectively from the medical records of patients with malignant pleural mesothelioma treated at Department of Pulmonary Diseases University Hospital Split during the 2000–2007 period. A total of 137 new cases was recorded with the mean incidence of 3.55/100 000 and the trend was increasing over years compared with 1992–1995 period in the same county when the mean incidence was 1.7/100000. Men accounted for 85.4% of all cases. The mean age of patients was 64.9±15.4 years. The majority of patients were occupationally exposed to asbestos (85.4%), 8.8% had environmental exposure, and 2.2% had domestic exposure. The type of household exposition was in 5.8% of patients. More than half of the cases were exposed to asbestos 31–40 years. The mean length of exposure was 28.87±15.63 years. The incidence of malignant pleural mesothelioma in Split-Dalmatian County has been obviously increasing due to the predominantly occupational exposure and it is reasonable to assume that it will remain high in the next two –three decades and to be a reason for concern and fear among the general population.

Key words: *mesothelioma, Split-Dalmatian County, Croatia, occupational exposure, environmental exposure, epidemiology*

Introduction

Malignant mesothelioma is a rare form of cancer that is found in the thin lining of the lung, chest, abdomen, and heart, associated with exposure to asbestos. The estimated annual crude incidence rates of malignant mesothelioma show marked variations from one country to another, in a range from 0.6–30 cases *per* million, being highest in Australia, Belgium and Great Britain[1]. The incidence of mesothelioma is directly related to the manufacture and use of asbestos. Although the incidence peak is approaching in the USA and Western Europe, in future decades the epidemic will shift towards countries that still manufacture or use large quantities of asbestos such as Russia, China, India, Canada, and many others[2]. Mortality continues to rise steeply (5%–10% per year) in most industrialized countries. It is estimated that by 2035 year 250 000 deaths in western European countries will be due to mesothelioma[2,3].

Exposure to asbestos can cause not only malignant mesothelioma, which is most commonly localized on the pleura, but also asbestosis (scarring of the lungs resulting in the loss of lung function that often progresses to

disability and death), lung cancer, cancers of the esophagus, stomach, colon, and rectum as well as pleural plaques, thickening and effusions[4–6]. The term asbestos designates a group of naturally occurring serpentine (chrisotyle) or amphibole minerals (crocidolite, amosite, anthophylite, tremolite and actinolite) that have extraordinary tensile strength, conduct heat poorly and are relatively resistant to chemical attack. Because of its specific technical properties, asbestos has found an extremely large variety of applications in about 3000 different products[7]. Most of these are materials that have been used in a wide range of manufactured goods, including roofing shingles, ceiling and floor tiles, paper and cement products, textiles, coatings, and friction products such as automobile clutch, brake and transmission parts.

The International Agency for Research in Cancer has clearly marked all types of asbestos among other carcinogenic substances from the »can cause cancer« group[8]. Asbestos is one of the most important occupational carcinogens causing about half of the deaths from occupational cancers[4,9]. Beyond the well-known association with occupational exposure, an increased risk was found for domestic exposure[6,10], as well as for residence near asbestos factories[6,11] and mines[12,13].

Asbestos-related diseases are one of the burning public health issuses in Croatia. These problems are especially important in the area covered by this study, i.e. Split-Dalmatian County, where a large part of the Croatian industry related to asbestos proccesing and use, such as two big shipyards and a large asbestos-cement product factory have been situated. So far, there has not been any study exploring the incidence of malignant pleural mesothelioma (MPM) in this area. Previous studies analyzed epidemiological situation in coastal Croatia (where the Split-Dalmatia County is only a part)[14] or in this county togheter with a neighbouring county[15]. The aim of this study was to assess the incidence and to highlight the epidemiological patterns of MPM in this particular area. We also intend to discuss briefly the history of asbestos-related issues in Croatia and development of current legislation related to asbestos.

Patients and Methods

The study was performed in 2008. Data on the incidence were collected retrospectively from the medical records of patients with MPM treated at Department of Pulmonary Diseases University Hospital Split during the 2000–2007 period. This Department is the only pulmology institution in a large area of south Croatia, thus the largest number of patients with various respiratory diseases are likely to be treated there. We included both inpatients and outpatients visiting Department for MPM counseling. Presumptive diagnosis was made on the basis of medical and occupational history, chest x-ray, and computerized tomography (CT) of the lungs (as needed). Confirmed diagnosis was made by hystology. Video-assisted thoracoscopy, pleuroscopy or open CT-guided pleural biopsy were performed to provide sufficient material for accurate histologic diagnosis. In some cases, effusion cytology was performed. Immunohistochemical analysis of biopsy material was also done in doubtful cases. The incidence rate was calculated based on the 1991 and 2001 census data[16]. The present study did not require the approval of an Ethics Committee.

Results

A total of 137 new cases of MPM during the 2000–2007 period were recorded at Department of Pulmonary Diseases University Hospital Split. The mean annual incidence was 3.55/100000 inhabitants, with a mean of 17 cases per year. The incidence fluctuated with time, but the trend was clearly increasing over years.The highest number of the cases was recorded during the last two study years (22 cases/year) (Figure 1).

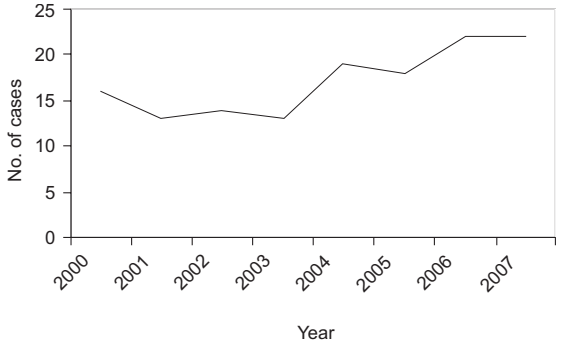

Fig. 1. Number of patients with malignant pleural mesothelioma in the Split University Hospital during 2000–2007.

MPM was diagnosed in 117 male and 20 female patients. Men accounted for 85.4% of all MPM cases (overall M:F ratio was 5.8:1). The mean MPM patient age was 64.92±15.4 (range 36–90) years. Out of the total number of patients, 8.7% were younger than 50, and 23.4% were older than 70 years. The majority of patients were in the 60–69 age group (38.7%), with only one case in a patient younger than 40.

The majority of patients were occupationally exposed to asbestos (85.4%), mostly working in shipbuilding industry (65.8% of those occupationally exposed), while workers from asbestos cement industry, construction industry and insulation industry accounted for 22.2%, 7.7% and 3.4% of occupationally exposed cases, respectively. One patient was fireman. Environmental exposure (housing or working near to asbestos industry) was recorded in 12 (8.8%) cases. Eight persons lived or worked at a distance less than 2 kilometers from asbestos industry, while four persons lived 2–5 kilometers away. Eight (5.8%) patients were living with asbestos workers (two wives and a son of asbestos workers). More than half of the cases (57.7%) had been exposed to asbestos for 31–40 years, 27% for 21–30 years, and 4.4% for less than 20 years. Ten (7.3%) patients were in the longest exposure

TABLE 1
CHARACTERISTICS OF PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA (N=137) IN THE SPLIT UNIVERSITY HOSPITAL DURING 2000–2007 PERIOD

Sex	N (%)
Men	117 (85.4)
Women	20 (14.6)
Age at diagnosis	
30–39	1 (0.7)
40–49	11 (8.0)
50–59	40 (29.2)
60–69	53 (38.7)
70–79	27 (19.7)
>80	5 (3.7)
Type of exposure to asbestos	
Occupation	117 (85.4)
– Shipyard industry	77 (56.2)
– Asbestos-cement industry	26 (18.9)
– Construction industry	9 (6.6)
– Insulation industry	4 (2.9)
– Fireman	1 (0.7)
Enviromental (housing or working near to the asbestos industry)	12 (8.8)
Domestic exposure (living with asbestos workers)	8 (5.8)
Duration of exposure to asbestos (years)	
<10	3 (2.2)
11–20	3 (2.2)
21–30	37 (27.0)
31–40	79 (57.7)
>40	10 (7.3)
Unknown	5 (3.6)

group (>40 years). The mean length of exposure to asbestos was 28.87±15.63 (range 2.5–42) years.

Study results are presented in Table 1 and geographical distribution of study cases is illustrated in Figure 2.

Diagnosis was made by histology in 128 (93.4%) cases. Video-assisted thoracoscopy or pleuroscopy was performed in 118 (86.1% of 137) cases, and open pleural biopsy under CT guidance was made in 10 (7.3%) cases to provide sufficient material for accurate hystologic diagnosis. On hystology, epithelial type prevailed with 60 (46.9%) cases, followed by sarcomatous and mixed types in 35 (27.3%) and 33 (25.8%) cases, respectively. Cytologic examination of the effusion was diagnostic in 9 (6.6%) cases.

Discussion

To the knowledge of these authors, this is the first study exploring the incidence of MPM in the Split-Dalmatian County where have been the largest concentration of asbestos pollution in Croatia (two large shipyards, factory of asbestos products and ship breaking yard). It is the second most inhabitant county (out of the 21 Croatian counties) with nearly 464 000 inhabitants situated in the south of Croatia, at the Adriatic Sea.

Fig. 2. Geographical distribution of malignant pleural mesothelioma in Split and Dalmatia County during 2000–200 select period. Black rectangle – shipyard, Black ellipse – asbestos-cement product factory, Black spot – one patient with malignant pleural mesothelioma who worked in asbestos industry or lived at distance up to 5 kilometres of asbestos industry.

This study showed that 3.55/100 000 people in the study area were diagnosed with MPM during the 2000–2007 period. The highest number of cases was recorded in the last two study years. A previous two studies in this county together with the neighboring one during the 1991–2000 period and 1992–1995 period showed a mean incidence of MPM of 1.53 *per* 100 000[15] and 1.7 *per* 100 000[17] respectively. Curin et al reported a MPM incidence of 1.4/100000 during 1991–1997 period in a much larger part of the Croatian coast than that covered by this study. In Northern Croatia, the MPM incidence was found to be 0.4/100000, which is even smaller[14]. According to the Croatian Cancer Registry, during 2000–2005 (latest data available), 289 cases of MPM were recorded in whole Croatia, with a mean incidence rate of 1.1/100 000 inhabitants. 3.6% of MPM patients lived in the same household with people professionally exposed to asbestos who would brought their working suits at home In comparison with previous studies the incidence of MPM has been obviously increasing in the study area, especially in recent years, by far exceeding the average rates in Croatia and in many countries worldwide[1]. There are several possible explanations why this county has been a Croatian hot spot in regard to asbestos-related diseases.

Two shipyards, ship breaking yards and the only Croatian asbestos-cement product factory are located in the area. The asbestos-cement product factory started working in 1921, employing generations of people from the surrounding area. Asbestos dust was released to the at-

Fig. 3. Unprotected asbesos waste dumped in factory yard.

Fig. 4. Unprotected dump with asbestos waste on the hills located several kilometers from asbestos factory.

mosphere for a long period. A mixture of asbestos was used, mostly composed of crocidolite asbestos which is believed to be more carcinogenic than other asbestos types[18,19]. After decades of intensive manufacture of asbestos products, it stopped working in 2006. Some amount of crude asbestos, asbestos residuals, sludge from waste water disposal system, and unsold final products (asbestos tubes) were left in the factory yard (Figure 3). In September 2007 the first phase of the asbestos cement waste removal from the factory was finished by disposing the waste to a predefined location[20]. However, the plan of asbestos waste management was a subject of discussion with local people and some local associations for environmental protection, which led to denunciation of the authorities responsible for remediation plan to the International Labor Organization and European Parliament[21]. In the shipyards, which have still been active, asbestos was widely used from the 1950s to the late 1980s. Those years were the period of huge pollution of the working and living environment, because of the heavy production, poor protection at work and unsatisfactory working hygiene. The whole study area underwent rapid urbanization and industrialization after the 1950s, along with a great increase in traffic[15]. It is currently stated that the time elapses between the initial asbestos exposure and the diagnosis of MPM is 20–50 years[1,7]. It is reasonable to assume that the incidence of asbestos-related diseases will grow, not only in terms of professional exposure but also through household contacts of individuals with occupational exposure as well as in the general population, while a decrease in the incidence of MPM in this area may not be reached for a long time. Second problem are remaining wild dumps of asbestos materials that are not sanated and are continuous source of asbestos pollution (Figure 4).

Our study results showed a high male predominance of MPM (85.4%), while the male to female ratio of 5.8:1 exceeded that reported for mesothelioma (4:1)[14]. It may be explained by the higher occupational exposure of men in shipyards and asbestos-cement industry, which have been mostly located in this county. However, we assumed that the actual MPM incidence in women must be higher than the observed one. The diagnosis is more difficult to make in women because they are not usually occupationaly exposed and MPM is not on the high position among differential diagnoses and there may be confusion with metastasis pleural diseases[6,22].

The majority of our patients were in the >60 age groups (62%) and exposed to asbestos 31–40 years before (57.7%), as shown in other studies[4,15]. This is in accordance with the known long latency period of MPM and the fact that exposure levels in the past were considerably higher than those received today. All asbestos-related diseases are dose-related: the higher the concentration and duration of exposure, the higher the prevalence and mortality of the diseases[19]. However, one patient was 36 years old, employed in the shipyard, with exposure of 2.5 years. The level of exposure could not be identified. Although a long latency period is usually necessary to develop MPM, the natural history of mesothelioma shows that the tumor may develop even after very short exposure to asbestos as in this case[1]. More than 85% of cases had a history of occupational exposure to asbestos or were presumably exposed to asbestos (construction workers). The results showed that the incidence of MPM most probably correlate with occupational exposure to asbestos in our population. The distribution of mesothelioma exactly reflected the location of asbestos industries, as postulated in other studies[1,14,23]. However, 8.8% of our patients had environmental exposure, while 5.8% of patients had householding exposure living with workers employed in asbestos industry. Residential exposure is well documented and it is decreasing with distance from asbestos sources. It has also been suggested that environmental exposure causes a greater risk than domestic exposure[11]. Eight of our patients were family members of asbestos workers. This risk may be the result of exposure to asbestos dust brought home on the clothing and hair of asbestos workers, as suggested elsewhere[6,11]. The fiber concentration in domestic exposure may be very high. Brushing clothes may give peaks of ≥100 fibers/ml[24]. Ordinary vacuum cleaning is not effective in removing asbestos fibers, which can remain for years in the house

and be airborne again whenever disturbed[6]. The type of exposure could not be recognized in four patients but studies show that once emitted to the atmosphere, asbestos fibers may travel considerable distances owing to their aerodynamic properties. As these fibers undergo no chemical breakdown, washout by rain or snow is the only cleaning mechanism[6,7]. Another possible reason for developing MPM is the fact that asbestos is still in place in many buildings and continues to give rise to exposure to both chrysotile and amphiboles during maintenance, alteration, removal and demolition[4]. The people living or working in buildings where asbestos has been used in construction or otherwise might well have been exposed to a high concentration of airborne asbestos fibers once or many times in their lives and in most instances unknowingly[6]. This includes most of us!

Several possible limitations of this study should be noted. Data were collected from medical records. The patients were not interviewed again for the purpose of the study. However, collection of detailed medical history of these patients is the routine practice. Assessment of exposure to asbestos and its effect was qualitative rather than quantitative, because the latency period before symptoms and diagnosis of mesothelioma can be very long, as noted in another study[14]. We cannot present the results of asbestos dust measurement in the environment during the period of exposure of our patients because it was not systematically done. These measurements were performed in the asbestos-cement product factory where the concentration of asbestos fibers in the air was usually 3–20 higher than the maximal allowable concentration, especially in asbestos stocks[18]. The maximal allowable concentration in the work environment is limited to 0.1 fiber/cm^3 for tremolite asbestos, 0.2 fiber/cm^3 for crocidolite and antophillite, 0.5 fiber/cm^3 for amosite and 2 fibers/cm^3 for chrysolite and actinolite, but the fibers are not physically specified[25]. In the regulations of many countries as well as in some international recommendations, asbestos fibers to be measured are defined as those equal to or longer than 5 μm and havnig diameters up to 3 μm with an asepct ratio equal to or greater than 3:1[6,7,26]. There is no allowable outdoor concentration in Croatia or in EU. However, the measurement of asbestos dust should be performed systematically for evaluation of both occupational and non-occupational exposure.

In spite of this limitation, this study clearly showed the incidence rate of MPM in the area to be on an increase as compared with previous studies and to greatly exceed the incidence rates in Croatia and in many other countries due to concentration of asbestos industry. The longstanding history of asbestos processing and use in the area has obviously led to high morbidity at individual level as well as enviromental pollution at the community level. There is great concern about future trend of the mesothelioma epidemic.

Conclusion

The incidence of MPM in southern Croatia has been obviously increasing due to the predominantly occupational exposure and it is reasonable to assume that it will remain high in the next decades because latency of asbestos-related and MPM is very long, even more then 40 years. After that period we hope it would be present only rare form MPM because prohibiton of production and utilisation of asbestos products and materials. Asbestos-related issues, especially in terms of increasing MPM, will continue to be a reason for concern and fear among the general population.

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MALIGNI MEZOTELIOM PLEURE: GORUĆI PROBLEM U SPLITSKO-DALMATINSKOJ ŽUPANIJI

S A Ž E T A K

Bolesti vezane uz izloženost azbestu su jedan od gorućih javnozdravstvenih problema širom svijeta. U ovom radu su analizirana epidemiološka obilježja malignog mezotelioma pleure u Splitsko-dalmatinskoj županiji, gdje je smješten najveći dio hrvatske azbestne industrije. Također je ukratko predstavljena povijest problema vezana uz izloženost azbestu kao i razvoj prateće legislative. Podatci o incidencije su retrospektivno prikupljeni iz povijesti bolesti oboljelih od malignog mezotelioma pleure Odjela za plućne bolesti Kliničke bolnice Split tijekom 2000–2007. godine. Ukupno je zabilježeno 137 novih slučajeva što čini prosječnu incidenciju od 3,55/100 000 stanovnika s trendom povećanja broja oboljelih tijekom promatranog razdoblja. Među oboljelima su prevladavali muškarci (85,4% od svih oboljelih). Prosječna starost bolesnika iznosila je 64,92±15,4 godina. Većina bolesnika bila je profesionalno izložena azbestu (85,4%), 8,8% bolesnika su bili izloženi u okolišu dok su 2,2% bolesnika bili izloženi u kućanstvu. Kod 3,6% bolesnika nije bila poznata vrsta izloženosti. Više od polovice bolesnika su bili izloženi azbestu 31–40 godina, dok je srednja dužina izloženosti iznosila 28,87±15,63 godina. Incidencija malignog mezotelioma pleure u Splitsko-dalmatinskoj županiji je u porastu, većinom kao rezultat profesionalne izloženosti te je vjerojatno da će biti visoka i u slijedećim desetljećima. Problemi vezani uz izloženost azbestu će, vjerojatno, i dalje biti razlog za zabrinutost i strah javnosti.