MINI-REVIEW

Malignant Mesothelioma in Eastern Asia

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Abstract

Relatively low numbers of malignant mesotheliomas have been reported from Eastern Asia. In order to explore the causes of this fact, the available data on mesothelioma incidence/mortality in five countries (Japan, South Korea, Taiwan, Hong Kong, and Singapore) were reviewed. Data on the industrial histories of the above countries were also examined. Mesothelioma incidence was low, despite a history of high shipbuilding and port activities, in which heavy exposure to asbestos generally has occurred. Underestimation of mesothelioma could partly explain the above discrepancy. Moreover, in some areas a sufficient latency period for mesothelioma development may have not yet elapsed, due to recent industrialization. However, other possibilities have to be considered. The cancer epidemiology in Eastern Asia differs deeply from that seen in Western countries, an indication of differences in etiologic factors of cancer as well as in co-factors. In addition, the oncogenic spectrum of asbestos is wide, and not completely defined. In a very different milieu from that of Western countries, asbestos could preferentially hit targets other than serosal membranes.

Keywords: Asbestos - malignant mesothelioma - epidemiology - diagnosis - geographic pathology - Eastern Asia

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Introduction

During the last decades, malignant mesothelioma, once a very rare entity, showed an impressive rise in incidence in various countries (Bianchi and Bianchi, 2007; Delgermaa et al., 2011; Park et al., 2011). Mesothelioma incidence/mortality shows extreme variations from one country to another (Bianchi and Bianchi, 2007). The geographic distribution of the tumor is relevant with reference to its etiology. Various studies have revealed a relationship between mesothelioma incidence at a country level and consumption of asbestos in the previous decades (Tossavainen, 2003; Tossavainen, 2004; Lin et al., 2007; Nishikawa et al., 2008). Moreover, in a given country the areas with high mesothelioma incidence exactly correspond to the location of the industries and activities, in which asbestos use has been heavy (Bianchi and Bianchi, 2007).

Since many years, it has been noted that in Eastern Asia the incidence of mesothelioma is very low, when compared with that of Western countries. This topic has been matter of investigation and debate (Giarelli and Bianchi, 2000; Bianchi and Bianchi, 2007; Le et al., 2011). Various reasons have been alleged to explain this finding, but the fact has remained not completely clear. In the present study we examine the available data on mesothelioma incidence in some countries of Eastern Asia. In addition, we reviewed the industrial history of the above countries.

Japan (population 127,937,000)

In Japan, the mortality from pleural cancer was very low until early 1990s, with less than 200 reported deaths in 1991 (Morinaga and Shinohara, 2011). In the following years there was a progressive increase in mortality from mesothelioma (all sites) with 500 cases in 1995, and 1,209 in 2010 (Morinaga, 2012).

The very low mesothelioma incidence in Japan until 1990s is at odds with the industrial history of the country. Low import of asbestos in the first half of the 20th century has been alleged to explain the low mesothelioma incidence, but the argument is not very convincing. The early asbestos industries started in Japan in 1880s (Hiraoka, 1993; Yokoyama, 1993). Moreover, shipbuilding activity was intense in Japan along the 20th century. At the end of 19th century and at beginning of 20th century, many ships for Japanese Navy were built in Europe, mostly in the United Kingdom. In the following decades a number of warships were built in Japanese shipyards, at Yokosuka, Kure, etc. The merchant fleet of Japan was also important, being in 1939 the third in the world. The amounts of asbestos imported by Japan in 1920s and 1930s seem to have been not relevant. However, in such period asbestos mined in Korea, at that time annexed to Japan, was used in shipbuilding (Paek and Choi, 2002). At the end of 1930s, in expectation of an embargo, Japan stocked various raw materials. These included asbestos. In the second half of the 20th century, an impressive increase in shipbuilding occurred in Japan (Giarelli and Bianchi, 2000). In this context, it is plausible that a widespread and heavy exposure to asbestos has involved large numbers of workers in Japan. Various studies conducted throughout the country on asbestos exposure markers (pleural plaques and lung asbestos

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bodies) have documented that such an exposure actually has occurred (Kimizuka and Hayashi, 1983; Ohyagi et al., 1985; Kohyama, 1989; Hiraoka et al., 1990; Shishido et al., 1990; Horii et al., 1992; Kishimoto, 1992; Tamura et al., 1992; Yano et al., 1993; Murai et al., 1995; Murai et al., 1997). In particular, various investigations showed the high level of asbestos exposure in the Japanese shipyards (Kishimoto et al., 1989; Natori et al., 1998; Kurumatani et al., 1999).

Cases of pleural and peritoneal mesothelioma were already diagnosed and reported in Japan in the 1950s (Matsunaga, 1952; Iwasaki et al., 1955; Utsumi, 1956). However, in surveying the Japanese literature until 1979, Matsukuma et al. (1982) found only four mesotheliomas associated with asbestosis. In 1983 Baba surveyed the Annual Report of Pathological Autopsy Cases for the period 1974-1980. During this period, 222 malignant mesotheliomas (145 pleural) were examined at autopsy in Japan. Occupational data were available for 54% of pleural mesotheliomas, the occupations of clerk or teacher being the most prevalent jobs in this series. Analysis of autopsy data collected in Japan in the period 1974-1993 (Aizawa et al., 1997) showed 939 primary malignancies of the pleura, and 579 primary malignancies of the peritoneum. Studies conducted in some areas of Japan, where major shipbuilding installations are located (Miura et al., 1999; Kishimoto et al., 2004), identified relatively low numbers of mesotheliomas, if compared with similar studies in Europe (Bianchi et al., 2001; Bianchi et al., 2004).

South Korea (population 48,755,000)

The number of mesothelioma cases registered at the Cancer Registry was extremely low in the early 1980s (Paek and Choi, 2002). In the following years there was an increase with 40-50 cases registered in the period 1993-2000 (Paek and Choi, 2002).

In the period 1998-2002 a total of 216 malignant mesotheliomas were notified to the Korea Central Cancer Registry (43.2 per year) (Lee et al., 2009). Between 1996 and 2006, 334 deaths were attributed to malignant mesothelioma in South Korea (Lee et al., 2009).

Jung (2011) has recently reviewed the experience of malignant mesothelioma surveillance in South Korea. In the period 2001-2010 a total of 479 cases were reported. The number of reported cases showed relevant fluctuation in the period with the lowest figure in 2002 (19 cases), and the highest in 2007 (98 cases). An occupational exposure to asbestos was detected in 37% of the cases. Shipbuilding emerged as the source of exposure in some cases only.
The history of asbestos use in Korea has been reviewed by Paek and Choi (2002). Many asbestos mines were active in Korea in 1930s and until 1945. During World War II, the chrysotile mine of Kwang-Chun employed more than 1,000 workers. Asbestos production was very low in the following decades and increased in the late 1970s, reaching about 16,000 tons in 1982. Asbestos import was high in the 1970s, and reached the highest values in 1992 with 95,476 tons. The import decreased after 1997. The principal uses of asbestos in Korea were manufactures of construction materials, asbestos textile and brake linings. It should also to be observed that Korea became a major shipbuilder in the last decades.

Taiwan (population 23,190,000)

Lee et al. (2010) have analyzed the data of Taiwan Cancer Registry. Between 1979 and 2005 a total of 423 histologically verified malignant mesotheliomas were found. In the study the cases without histopathological proof were not considered and these comprised 242 cases. The incidence of malignant mesothelioma increased during the observation period, but it remained low also in the most recent period.

About 20-40,000 metric tons of asbestos were imported annually to Taiwan in the period 1970-1990 (Chang et al., 2002). In 1987, 41 asbestos factories were active in Taiwan with a total of 471 workers (Chang et al., 2002).

During the last decades of the 20th century, shipbuilding was important in Taiwan, with ship orders being over 3 million tons in the period June 1981-May 1982 (Encyclopaedia Britannica, 1983).

Hong Kong (population 7,125,000)

In 1983 Lam et al. described three patients with malignant mesothelioma (pleural in two cases, pericardial in one) and one patient with asbestosis and small cell carcinoma of the lung. All the patients had histories of occupational exposure to asbestos. The authors emphasized that this was the first report of asbestos disease in Hong Kong. Moreover, a review, made by one of the researchers, of 5,984 necropsies carried out at the University Department of Pathology, Queen Mary Hospital, between 1964 and 1976, showed no cases of malignant mesothelioma or asbestosis. In commenting their findings, the authors said that, while there were many workers exposed to asbestos in industries in Hong Kong, the problem of asbestos-related disease had received little attention. They believed that the four cases over a period of six years were almost certainly an underestimate of the true picture.

In 2006 Chang et al. investigated the epidemiology of mesothelioma in Hong Kong from 1988 to May 2002 by reviewing the medical records of 12 Hong Kong Hospitals. They identified 67 mesothelioma patients, with high prevalence among workers in shipyards. The estimated annual incidence rate was one per million.

Tse et al. (2010) reviewed the cases of malignant mesothelioma registered at the Hong Kong Cancer Registry. During the period 1976-2006, a total of 199 mesothelioma cases had been diagnosed (137 in males, and 62 in females). The age-standardized incidence rates rised markedly in the observation period, with the highest values among people aged 70 years or more. Among males, the incidence rate peaked in 2004 with 3.86 per million. Tse et al (2010). estimated that the average of asbestos consumption was high in Hong Kong in the 1960s and in the 1970s (6.14 kg/capita/year).

Hong Kong is one of the largest ports in the world. It has been reported that over 200,000 ships visit this port

each year. Ship maintenance and ship repair is usual in a large port, and this indicates that heavy asbestos exposure is highly probable. If this is true, mesothelioma incidence in Hong Kong seems to be relatively low.

Singapore (population 5,182,000)

Ho et al. (1987) reported that 16 cases of malignant mesothelioma had been notified to Singapore Cancer Registry between 1968 and 1984. The authors restricted their study to nine Singapore residents. The remaining cases were not considered because the patients were foreigner and had left the country, or because the mesothelioma diagnosis was not confirmed on a review of histology. Ho et al. (1987) calculated a crude annual incidence rate of 0.43 per million. Of the nine cases, five were peritoneal and four pleural. Occupational histories were available in six cases only. All these patients had histories of exposure to asbestos, although the authors were doubtful on this point.

In the period 1993-2002, 62 pleural and 11 peritoneal mesotheliomas were registered at the Singapore Cancer Registry (Yip et al., 2011). A recent study (Yip et al., 2011) was mainly devoted to the clinical aspects in 39 patients with malignant pleural mesothelioma, seen at the National Cancer Centre in Singapore. Strangely, in such group an occupational history of asbestos exposure was obtained in 33% only of the cases.

Singapore is one of the largest ports in the world. Like in the case of Hong Kong, the low incidence of mesothelioma seems to be in contrast with the port activities.

Interpretation

The mesothelioma incidence in Eastern Asia is low, when compared with that reported from Western countries. Furtherly, a discrepancy is apparent between mesothelioma epidemiology in Eastern Asia and the industrial history of the region. To explain this discrepancy, various reasons have been proposed, including underdiagnosis/underregistration of mesothelioma, sufficient latency periods not elapsed due to more recently industrialization of Eastern Asia, use of different types of asbestos. Various researchers in Eastern Asia have said that little attention had been devoted to asbestos disease in their countries, and that mesothelioma was very probably a misdiagnosed entity (Lam et al., 1983; Murayama et al., 2006; Morinaga, 2009; Lee et al., 2009). A lot of clues seem to confirm that mesothelioma is actually underestimated in Eastern Asia. For instance, in Japan many problems in the registration of deaths from mesothelioma have been encountered in the past (Murayama et al., 2006; Morinaga and Shinohara, 2011). In Korea Kim has described some cases of malignant pleural mesothelioma, in which a misdiagnosis caused a delay in the correct identification of the tumor, varying between one month and two years (Kim, 2011). In China a high rate of misdiagnoses was observed by Chen et al. (2012) in analyzing a series of 45 malignant pleural mesotheliomas.

The hypothesis that sufficient latency periods have not yet elapsed in some Asian areas, because industrialization is recent, deserves also attention. It is currently affirmed that development of mesothelioma requires 20-40 years since first exposure to asbestos. However, many studies showed substantially longer latency periods, with means close to 50 years (Bianchi et al., 2002; Hilliard et al., 2003; Bianchi et al., 2007; Ohar et al., 2007). Therefore, it is possible that sufficient latency periods have not yet elapsed in some areas. Anyway, this reason is not valuable in the case of Japan, a country already highly industrialized in the first half of the 20th century. Regarding the role of the different asbestos varieties, the question remains controversial. All the types of asbestos are recognized as oncogenic (IARC, 2012). Even if differences in the oncogenic potential of the different asbestos types may exist, in a large majority of settings the exposure was mixed, involving both chrysotile as well as amphiboles.

It remains doubtful if the low incidence of mesothelioma in Eastern Asia might entirely be explained by the above reasons. It is opportune, however, to consider other possible explanations.

Studies conducted over five decades showed that mesothelioma is almost invariably related to asbestos. Nevertheless, relatively low percentages of people exposed to asbestos develop the tumor (Bianchi and Bianchi, 2012). This fact clearly indicates that asbestos is a necessary but not sufficient condition in the mesothelioma pathogenesis. On the contrary, co-factors play a role in the development of asbestos-related mesothelioma (Bianchi and Bianchi, 2008). If the sequence of events that lead from the entrance of asbestos fibers into the human tissue to the development of mesothelioma is regularly observed in Western countries, this does not necessarily mean that the same sequence has to be seen in Eastern Asia. In a number of malignancies the geographical patterns in Eastern Asia are markedly different from those observed in Western countries. This is true for carcinomas of many organs such as lung, larynx, breast, stomach, colon-rectum, liver, prostate, uterus (endometrium), ovary, bladder, nasopharynx, kidney as well as for lymphomas, leukemia and melanoma (Stewart and Kleihues, 2003). This suggests that, despite globalization, the etiologic factors of cancer (genetic, environmental, interactions genetic-environmental) are not the same in the different regions of the world.

In addition, it is well known that asbestos may induce cancer in various sites (serosal membranes, lung, larynx, ovary) (IARC, 2012). However, the entire oncogenic spectrum of asbestos remains not defined. The recent IARC Monograph says that the literature data suggest a relationship between asbestos exposure and other malignancies, such as carcinomas of pharynx, stomach and colon-rectum. The results of some recent investigations corroborate such an idea. In a cohort study on 2,024 people exposed to asbestos, conducted in France, beside a raised risk for mesothelioma and lung cancer, a high risk for colorectal carcinoma emerged (Clin et al., 2011). A case-control study on stomach carcinoma, performed in Spain, showed a raised risk among men exposed to asbestos (Santibañez et al., 2012). In addition, a role of asbestos has been suspected in the genesis of liver carcinoma (Bianchi

et al., 2002) and non-Hodgkin lymphoma (Bianchi et al., 2010).

In this context, one should ask if in a very different milieu, asbestos might preferentially hit targets other than serosal membranes.

The above considerations are supported by the results of an investigation recently conducted in the Dayao area, China (Wei et al., 2012). The study showed that naturally occurring asbestos may significantly elevate the mortality rates of various malignancies, including nasopharyngeal and laryngeal cancer, intestinal cancer, lung cancer and mesothelioma.

In conclusion, to attribute the low number of mesotheliomas in Eastern Asia to underdiagnosis or to recent industrialization only, may represent an oversimplification of the problem. The low mesothelioma incidence in this region may be a more complex event than

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