

Kishimoto

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Shipyard

# The Relationship Between Lung Cancer and Asbestos Exposure\*

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This study supports the theory that asbestos exposure may be implicated in a recent upsurge of terminal lung cancer cases in Kure, Japan. The number of asbestos bodies found in the lung during autopsy of 158 subjects from 1984 to 1986 suggests that 70.4 percent of the 51 diagnosed lung cancer cases could be attributed to asbestos exposure. Of the 107 subjects in whom death was not caused by cancer, 38.4 percent had significant asbestos exposure. Types of asbestos bodies found in diagnosed lung cancer cases were analyzed using scanning electron microscopy and x-ray analyzer. Chrysotile was the most widely found component.

but amphiboles such as crocidolite and amosite also were detected. Residents of Kure had high exposure to the inhalation of asbestos bodies, possibly related to the upsurge in lung cancer deaths. In our earlier report, asbestos exposure was implicated in the increased incidence of malignant mesothelioma in Kure, an active Japanese shipbuilding port since the 1920s. Our current findings indicate that asbestos exposure may be a pathogenic factor in lung cancer in world seaports where asbestos exposure has been prevalent. (*Chest* 1988; 94:486-90)

From 1984 through 1986, there was a significant increase in the rate of death from lung cancer in Japan. This increase is particularly evident in the male population and in certain geographic areas including Kure, Japan. We previously reported a similar increase in the death rate from malignant mesothelioma and provided evidence for an etiologic relationship to asbestos exposure. In the current study, our data suggest that asbestos exposure may also be the underlying cause of the recent upsurge in lung cancer.

## MATERIAL AND METHODS

In the three-year period from 1984 to 1986, autopsy was performed at Kure Kyosai Hospital on 158 patients who had resided in the city or suburbs of Kure, Japan. Fifty-one cases were of lung cancer and seven malignant mesothelioma, and 100 were noncancerous. The number of asbestos bodies in the lung tissue of these 158 cases were counted by the modified method of Smith and Naylor.<sup>1</sup> Briefly, 1 g of lung tissue (inferior lobe without tumor involvement) was lysed in sodium hypochlorite for 48 hours. Asbestos bodies were separated by the use of equal volume (20 ml) of chloroform (Wako) and 50 percent ethanol (Wako) and centrifuged at 150 g for five minutes. The bottom fraction was filtered on a 5- $\mu$ m Millipore filter. Finally, the number of asbestos bodies were counted on the filter by light microscopy ( $\times 200$ ).

For cases with lung cancer, we recorded sex, age, histology, lateral involvement, originating lobe, smoking history, occupational history, and the duration of asbestos exposure. Detected asbestos bodies were coated with carbon, then analyzed by using scanning electron microscopy (T-330, JEOL) and x-ray analyzer (Seiko). The type of asbestos bodies was determined according to the UICC standard reference.<sup>2,3</sup> For identification, we measured the types and percentages of metals in the asbestos bodies and determined the kind of asbestos bodies. We analyzed at least 20 asbestos bodies in each

case. Asbestos bodies were also counted in noncancer cases: 15 cases of cerebral vascular accident (CVA), 27 myocardial infarction, eight tuberculosis of the lung, 21 liver cirrhosis, 15 pneumonia, and 11 others (two hypoplastic anemia, two sepsis, three renal failure, three diabetes mellitus, and one suicide). For control, we referred to the number of asbestos bodies found in autopsied lungs in other parts of Japan and estimated the baseline of the significant number of asbestos bodies per 1 g of lung tissue.<sup>4,5</sup> In this study we used nonparametric analysis using the Krushal-Wallis one-way analysis of variance and the multiple comparison method of Dun.<sup>6</sup>

## RESULTS

Figure 1 shows the number of asbestos bodies per gram of lung tissue in lung cancers, mesotheliomas, and noncancer patients. All patients with malignant mesotheliomas had asbestos bodies numbering more than 500/g of lung tissue, whereas 36 of 51 (70.6 percent) patients with lung cancer had more than 100/g (up to 381,025/g). This is significantly ( $p < 0.01$ ) higher than that of noncancer cases (38.6 percent). In the noncancer group there were 18 cases whose count of asbestos bodies exceeded 500/g. All of these cases had established occupational histories of asbestos exposure, but the other 36 patients did not have definite occupational histories of asbestos exposure.

Figure 2 shows the classification of cases with lung cancer according to sex. Of the six cases in women, two had more than 100 asbestos bodies/g. By contrast, 75.6 percent of cases in men had more than 100 bodies/g. The difference is statistically significant ( $p < 0.01$ ). All of the men had occupational histories of asbestos exposure.

Figure 3 classifies the cases of lung cancer according to histologic diagnosis: 21 cases of squamous cell carcinoma, 24 adenocarcinoma and large cell carcinoma, and six small cell carcinoma. The average number of asbestos bodies in the squamous cell type

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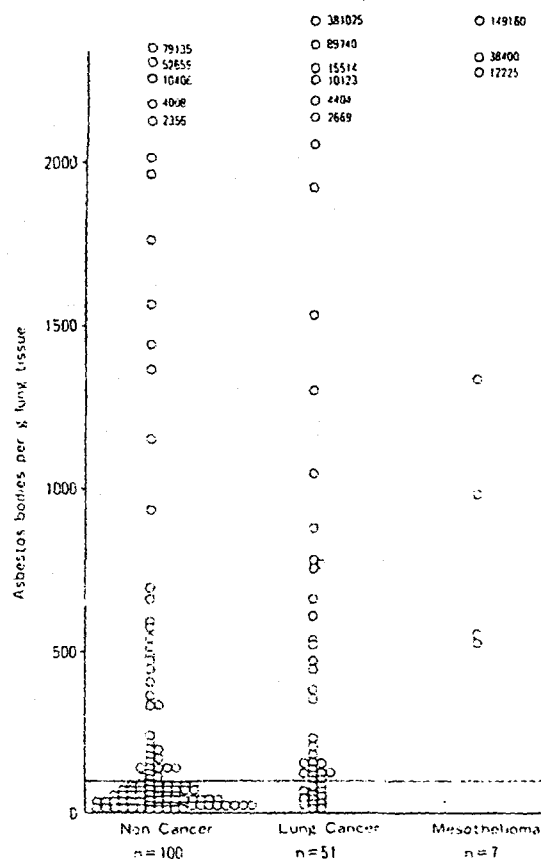


FIGURE 1. Number of asbestos bodies per gram of lung tissue in cases without cancer and in patients who died from lung cancer and mesothelioma. Number of asbestos bodies in cases with lung cancer and mesothelioma is significantly higher ( $p < 0.01$ ) than that of noncancer cases: lung cancer,  $10,432 \pm 7,778$ ; noncancer,  $151 \pm 28$ ; mesothelioma,  $37,115 \pm 19,723$ .

was higher than those of other types, especially compared with the small cell type. Cases with right lung involvement ( $4,065 \pm 1,974$ ) had more asbestos bodies than those of the left side ( $19,952 \pm 19,028$ ), and those in the superior lobe ( $17,481 \pm 13,338$ ) more than inferior ( $698 \pm 238$ ). According to the smoking history of these 51 lung cancer patients, 36 were more than 400 by the Brinkman Index (BI).<sup>7</sup> The women patients were not heavy smokers, but 78.6 percent of the men were heavy smokers. Occupational history indicated that 25 of these men worked in the Japanese naval shipyard before or during World War II. Another six patients had occupational histories in other shipyards. A total of 36 cases had definite history of asbestos exposure. The duration of asbestos exposure in these cases was six months to 48 years (average, nine years). Occurrence of death following initial exposure was 15 to 48 years (average, 27 years). Chrysotile was the major component of asbestos bodies

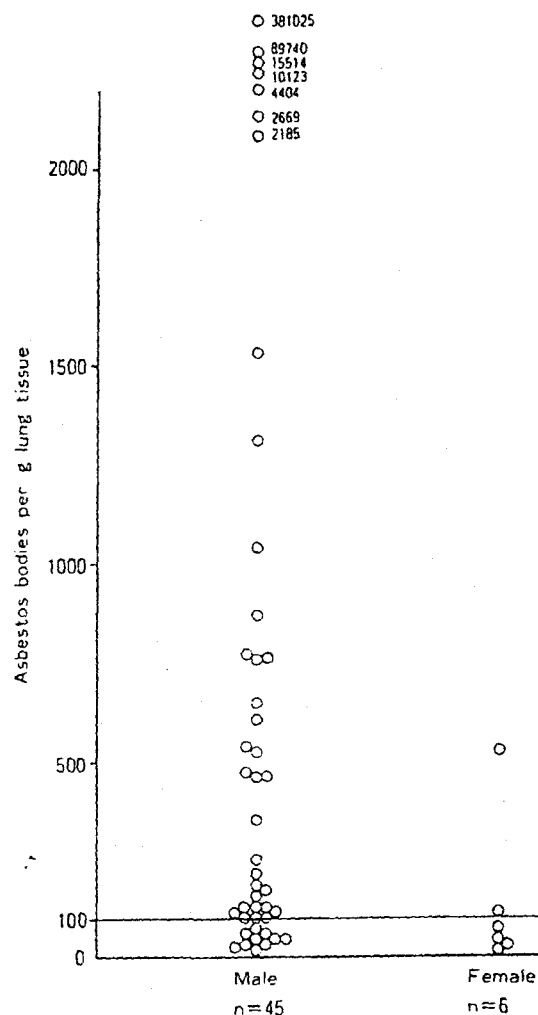


FIGURE 2. Distribution of lung cancer according to sex. The 6 cases in women had considerably fewer asbestos bodies than men. Occupational history in males may explain this difference. Male,  $11,339 \pm 8,450$ ; female,  $129 \pm 79$ .

detected in lung tissue of patients with lung cancer. Figure 4 shows typical results of analysis of an asbestos body found in a lung cancer case. According to the percentages of Mg, Ca, Fe, and Si, we determined this asbestos body to be chrysotile. Some crocidolites and amosites also were found. Ordinarily, we would expect to find these three types of asbestos in the same patient, but chrysotiles were the main component found in 70 percent of patients with lung cancer.

#### DISCUSSION

The incidence of lung cancer, which has recently increased in Japan, has shown a pronounced upsurge in specific regions such as Kure City in Hiroshima Prefecture, particularly in male patients (Table 1).

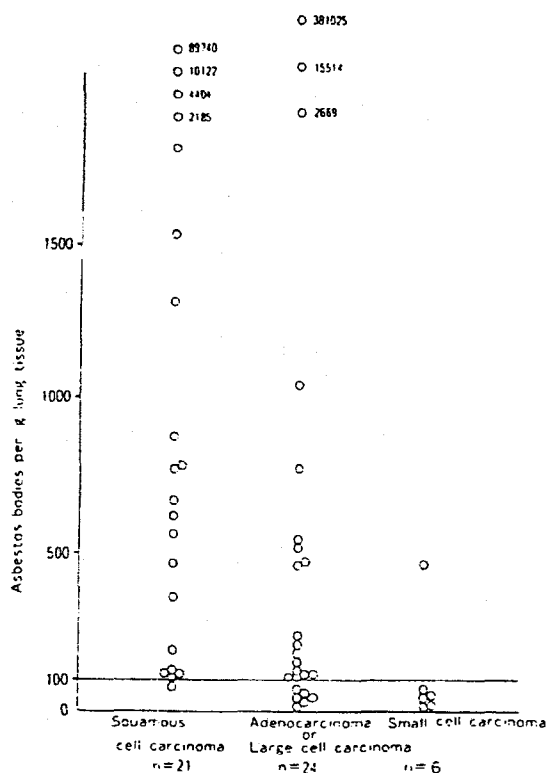


FIGURE 3. Distribution of lung cancer cases according to histology. A higher number of asbestos bodies was seen in patients with squamous cell carcinoma and adenocarcinoma. There is a significant difference between squamous and small cell cases ( $p < 0.01$ ). Squamous cell carcinoma,  $6.121 \pm 4.675$ ; adenocarcinoma, and large cell carcinoma,  $13.518 \pm 12.865$ ; small cell carcinoma,  $104 \pm 53$ .

TN-5500/JXR-840 X-ray Analyser  
Cursor: 0.000KeV = 0 R01

Japan is a major industrial country in which asbestos minerals have been utilized for about 50 years. Since the 1920s, Kure's naval shipyards have been well-known, and shipbuilding has continued in Kure and its suburbs since 1945. Most male residents over 70 years old have had at least some occupational connection with naval shipbuilding in Kure.

We recently documented that the recent upsurge of incidence of malignant mesothelioma could be related to asbestos exposure.<sup>8</sup> This is consistent with several other reports demonstrating asbestos exposure in shipyards.<sup>9,10</sup> In the present study we extended our work to cancer of the lung. We evaluated 51 cases of lung cancer on whom autopsy was done in an attempt to relate the appearance of cancer to asbestos exposure. To estimate the extent of asbestos exposure, we set a limit of 100 asbestos bodies/g of lung tissue as the baseline. This measurement is high enough to compare the volume of asbestos bodies detected in any Japanese person with asbestos exposure<sup>4,5</sup> as well as to compare data with other reports.<sup>11,12</sup> According to this criterion, 70.6 percent of patients with lung cancer had more than baseline asbestos exposure than 38.6 percent of noncancer patients. In addition, almost all of them had an occupational history of work in Japanese naval shipyards. Therefore, it is likely that asbestos exposure is an etiologic factor in the recent upsurge in lung cancer in Kure City.

These patients were also heavy cigarette smokers (BI more than 400), and smoking is thought to be an important factor in pathogenesis of asbestos-induced lung cancer.<sup>13,14</sup> The latency of lung cancer after

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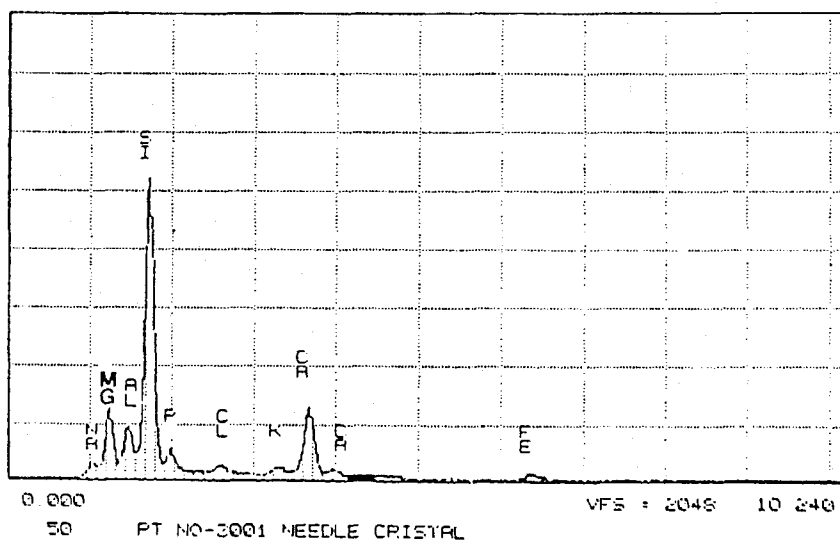


FIGURE 4. Typical analysis of an asbestos body from a lung cancer case. According to the UICC standard reference, we determined this body to be chrysotile.

Table 1—Cancer and Lung Cancer Mortality in Males Exposed to Asbestos in Kure, Japan, Compared with Other Parts of Japan, 1985-87

| Year                       | No. | Kure City | Hiroshima Prefecture | Average, Japan |
|----------------------------|-----|-----------|----------------------|----------------|
| 1985                       |     |           |                      |                |
| Total cancer cases in Kure | 431 |           |                      |                |
| Lung cancer cases in Kure  | 70  | 30.5*     | 25.9*                | 23.3*          |
| Male: Total cancer cases   | 255 |           |                      |                |
| Lung cancer cases          | 50  | 44.7      | 37.2                 | 34.6           |
| Female: Total cancer cases | 176 |           |                      |                |
| Lung cancer cases          | 20  | 17.0      | 13.1                 | 12.3           |
| 1986                       |     |           |                      |                |
| Total cancer cases in Kure | 427 |           |                      |                |
| Lung cancer cases in Kure  | 73  | 31.8      | 25.8                 | 23.8           |
| Male: Total cancer cases   | 281 |           |                      |                |
| Lung cancer cases          | 58  | 51.8      | 38.0                 | 35.3           |
| Female: Total cancer cases | 146 |           |                      |                |
| Lung cancer cases          | 15  | 12.7      | 14.1                 | 12.7           |

\*Per 10,000.

asbestos exposure is estimated to be more than 20 years.<sup>15</sup> Our data were consistent with those of Bohlig and Otto.<sup>15</sup> Three major kinds of asbestos bodies (chrysotile, crocidolite, and amosite) induce cancers. Amphiboles such as crocidolite and amosite are the major components of asbestos bodies thought to be involved in the pathogenesis of lung cancer.<sup>16,17</sup> Other articles describe chrysotile-induced lung cancer.<sup>18,19</sup> Interestingly, chrysotile is the major component in our cases, and crocidolites and amosites were dominant in only 30 percent of cases with lung cancer. In all of our cases, chrysotile and amphiboles were mixed together in cases of lung cancer, a result consistent with that of the Howard report.<sup>20</sup>

According to the histologic type, squamous cell carcinoma had a much higher incidence, and small cell types were rare in our series. Most cases originated on the right side, with higher incidence in the inferior lobe. Adenocarcinoma and inferior lobe origin were dominant in other reports of asbestos-induced lung cancer.<sup>21-23</sup> In long-term cigarette smokers, squamous metaplasia occurs and replaces the normal ciliary epithelium.<sup>24</sup> The presence of smoking history in addition to chrysotile exposure could be responsible for this discrepancy.

Some investigators have indicated that the baseline number of asbestos bodies in 5 g lung tissue is less than 100.<sup>5,25-27</sup> We think that this baseline is too low, and 100 per/1 gram lung tissue is a more realistic figure.

Geographically, Kure City is surrounded on three sides by mountains and on the fourth side by the Japan Inland Sea. Since the 1920s, shipyards have been the major economic resource of the city, and consequently exposure to asbestos has been universal. Because of the relative latency of asbestos-induced cancer, the upsurge in incidence of asbestos-induced cancer has

been expected to peak in the 1980s, and we think that the recent upsurge in lung cancer may be explained on this basis.

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The American Medical Association will present this conference, co-sponsored by other health professional organizations, at the Chicago Marriott Hotel, October 26-30. The purpose of the conference is to encourage development of programs that include the major components of prevention, education, case-finding, intervention, treatment referral, aftercare/monitoring and re-entry/retraining to encourage an increased level of funding for such comprehensive programs; and to better help those programs provide rehabilitative help while ensuring public safety. The conference will bring together the varying disciplines and organizations concerned with the impairment and well-being of health professionals and to stimulate the creation of working relationships among these based on common concerns and mutual respect so as to better utilize existing resources. In addition, the conference will provide a forum for the interchange of ideas and approaches that can be replicated to help programs function more effectively.

*The conference welcomes anyone involved, or wishing to become involved, in programs to identify, treat, rehabilitate or discipline health professionals suffering from alcoholism, drug dependence, psychiatric illness or other potentially impairing problems, such as hospital administrators, risk managers, and medical staff coordinators; licensing board members, staff, investigators; deans/faculty members from medical and dental schools, etc; residency training directors/programs directors and staff/professionals in training; spouses of physicians and other health professionals; professionals in recovery; treatment providers.*

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