A Case-Control Study of Lung Cancer with Special Reference to Asbestos Exposure

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A case-control study of lung cancer was carried out in Yokosuka City, Kanagawa Prefecture, the location of a pre-war Japanese Imperial naval factory and present site of a U.S. naval base. Cytologically or pathologically confirmed male fatal cases of lung cancer during the period of 1978 to 1982 in Yokosuka Kyosai Hospital were compared with a control group in the same hospital. Controls who died from causes other than cancer, pneumoconiosis, accident, or suicide were matched by age to the cases. Information that included occupational and smoking history was obtained by interviews with the families of the 96 cases and 86 controls. Major results were as follows: a) The relative risks of lung cancer associated with asbestos exposure and suspected exposure were 2.41 (p < 0.05) and 1.56, respectively, after controlling for age and smoking history, and the relative risk associated with smoking was 6.01 (p < 0.05) after adjusting for age and asbestos exposure. b) The age- and smoking-adjusted relative risks of lung cancer associated with asbestos exposure were 3.40 (p < 0.01) and 1.72 for Kreyberg groups I and II, respectively. Significantly elevated relative risk associated with smoking history was demonstrated for Kreyberg group I, but not for group II, after controlling for age and asbestos exposure.

Introduction

A number of studies have examined the relationship between lung cancer and shipbuilding, one of the major sources of asbestos exposure (1–4). Few epidemiological studies, however, have assessed the risk of lung cancer by histological type with asbestos exposure (5), although there are several reports on the histological distribution of lung cancer types among asbestos-exposed populations (6–10).

Several ecological studies have shown the positive relationship between shipbuilding and lung cancer mortality in Japan. Two of four cities in which Japanese Imperial naval factories were located showed a significantly higher lung cancer mortality than the national average (11), and cities and towns with shipyards have tended to have elevated mortality rates of lung cancer (12). Several studies have analyzed lung cancer among asbestos workers; however, none has dealt with exposure in shipyards, although shipbuilding has been one of the major industries in Japan. Thus, a case-control study with special reference to asbestos exposure mainly through shipbuilding was carried out in Yokosuka City, Kanagawa Prefecture, where a Japanese Imperial naval factory was located until the end of the Second World War, and which is now a U.S. naval base.

Yokosuka City is located at about 60 km south of Tokyo at the entrance of Tokyo Bay. The first shipyard there was established as early as 1853, during the last days of the Tokugawa Shogunate. In 1884, an admiralty port was established in the city, and the shipyard developed to Yokosuka Imperial Naval Factory in 1903. During the Second World War, about 70,000 workers, or one-fifth of the population of the city, were engaged in shipbuilding. After the war, Yokosuka Admiralty Port became a U.S. naval base, and the Imperial Naval Factory became a repair factory for the U.S. Navy.

Subjects and Methods

The lung cancer group consisted of male fatal cases diagnosed as having primary lung cancer confirmed histologically by cytological examinations of smears, surgical specimens, or autopsy specimens in Yokosuka Kyosai Hospital during the period from 1978 to 1982. The families of 116 of 129 eligible cases were included in this study. In the other 13 cases, the address was unknown. Male fatal cases without cancer or pneumoconiosis who died in the same hospital of causes other than accident or suicide and whose date of birth was nearest to each of the lung cancer cases were selected as controls. All cases and controls were Japanese.
The families of the lung cancer and control groups were interviewed by the authors, mainly at the family’s home, using a standardized questionnaire including detailed occupational history, work site, and smoking history. It was not revealed to the interviewees that the actual purpose of the study was to examine the association between lung cancer, smoking, and asbestos exposure. To avoid interviewer bias, the interviewers were not told whether the interviewee was a case or a control. History of asbestos exposure was categorized by the investigators who did not participate in the interview into “exposed,” “suspected,” and “not exposed” on the basis of occupational history and work site (Table 1). Table 1 is based on the prevalence of asbestos bodies in previous autopsy cases in Yokosuka Kyosai Hospital.

As all lung cancer cases were histologically confirmed, analyses were made by histological type: Kreyberg group I (squamous cell carcinoma, large cell carcinoma and small cell carcinoma) and group II (adenocarcinoma and others) (13).

Odds ratios adjusted for age, age and smoking history, or age and asbestos exposure were calculated to estimate relative risk. Mantel-Haenszel’s test (14) or the extended Mantel’s test (15) was applied to assess the statistical significance of odds ratios adjusted for confounding factors.

Results

Of the 116 pairs of subjects, the families of 96 lung cancer cases and 86 controls were successfully interviewed, and the findings were subjected to the following analyses. The histological types of lung cancer cases were mainly squamous cell carcinoma and adenocarcinoma, followed by large cell carcinoma and small cell carcinoma (Table 2). Thirty percent of the histologic diagnoses were obtained from specimens used in cytological diagnosis or obtained at surgical operation. The primary cause of death in the

Table 1. Examples of asbestos exposure categorization by occupational history and work site.

| Work site | Exposed | Suspected exposure | Not exposed |
|-----------|---------|--------------------|-------------|
| Imperial naval factory, U.S. naval base, shipyards | Plumbers, lathemen, boiler manufacturers, electricians, mechanics, assemblermen, sheet metal workers, welders, painters, repairmen, ship carpenters, airplane mechanics, other job site workers | Carriers, wireless operators, draftsmen, occupation unknown | Clerks |
| Construction site | Carpenters, scaffolding men, plasters and designers obviously related to naval factory | Carpenters, scaffolding men, plasters and designers working in Yokosuka | Carpenters, scaffolding men, plasters and designers not related to naval factory |
| Other | Boilermen, car mechanics pre-war taxi drivers, fishing boat sailors, electricians, mechanics | | |

Table 2. Histological types of lung cancer.

| Histological type     | Cases |
|-----------------------|-------|
| Squamous cell carcinoma | 33    |
| Small cell carcinoma   | 10    |
| Adenocarcinoma         | 34    |
| Large cell carcinoma   | 12    |
| Other                  | 7     |
| Total                  | 96    |

Table 3. Causes of death in control group.

| Cause of death         | Cases |
|------------------------|-------|
| Heart disease          | 23    |
| Cerebrovascular disease| 17    |
| Respiratory disease    | 14    |
| Liver disease          | 6     |
| Pulmonary tuberculosis | 7     |
| Renal disease          | 8     |
| Sepsis                 | 3     |
| Diabetes mellitus      | 2     |
| Other                  | 6     |
| Total                  | 86    |

Table 4. Sources of information.

| Source               | Cases | Controls |
|----------------------|-------|----------|
| Wife                 | 64    | 55       |
| Son or daughter      | 13    | 15       |
| Daughter-in-law       | 14    | 11       |
| Sibling               | 3     | 2        |
| Others                | 2     | 3        |
| Total                | 96    | 86       |

\[ \chi^2 = 1.037, \text{degrees of freedom} = 4 (p > 0.05). \]

case group was heart disease, followed by cerebrovascular disease, respiratory disease, and renal disease (Table 3). Information was obtained mainly from the wives of the subjects, followed by sons or daughters-in-law. There was no statistically significant difference in the source of information between the lung cancer and control groups (Table 4).

The age-adjusted relative risk of lung cancer associated with smoking was 6.52 ($p < 0.01$). The younger the age at which smoking was started, the higher the risk of lung cancer ($p < 0.01$). The risk of ex-smokers was comparable to that of current smokers, and the amount of smoking was not associated with relative risk. The age-adjusted relative risks of lung cancer associated with asbestos exposure and suspected exposure were 2.54 ($p < 0.05$) and 1.66, respectively (Table 5). Of 38 lung cancer cases with asbestos exposure, 32 had at some time engaged in shipbuilding.

Table 6 shows relative risks of all lung cancer types, Kreyberg group I and group II, adjusted for age and asbestos exposure or for age and smoking history as well as those adjusted only for age, in order to assess the effects of each factor independently.

The age- and asbestos-adjusted relative risk of all lung cancer associated with smoking history was 6.01 ($p < 0.05$). A much higher relative risk (13.51, $p < 0.05$) was noted for Kreyberg group I, while only a mild elevation of no statistical significance was shown for group II (relative risk = 1.64).

On the other hand, the age- and smoking-adjusted relative risk of all lung cancer associated with asbestos exposure was 2.41 ($p < 0.05$), and the risk increased with exposure level ($p < 0.05$). This pattern was more marked for Kreyberg group I (relative risk of 3.40 [$p < 0.05$] for asbestos exposure, with statistically
Table 5. Distribution of lung cancer cases and controls by smoking history and asbestos exposure in Yokosuka, Japan.

| Variable                  | Cases | Controls | Age-adjusted relative risk |
|---------------------------|-------|----------|-----------------------------|
| **Smoking history**       |       |          |                             |
| Nonsmokers                | 3     | 15       | 1.0                         |
| Exsmokers                 | 15    | 12       | 7.69*                       |
| Smokers                   | 78    | 59       | 6.52*                       |
| **Smoking dose**          |       |          |                             |
| Nonsmokers                | 3     | 15       | 1.00                        |
| Smokers                   | 1–19 cigarettes/day | 18 | 13 | 6.78* |
| 20 or more                | 69    | 53       | 6.42*                       |
| **Age when started smoking** |       |          |                             |
| Nonsmokers                | 3     | 15       | 1.00                        |
| Smokers                   | 30 years old or later | 2 | 1 | 7.70 |
| 20–29 years old           | 42    | 32       | 6.69*                       |
| Younger than 20 years     | 33    | 14       | 11.56*                      |
|                          |       |          | Extended Mantel test p < 0.01 |
| **Asbestos**              |       |          |                             |
| Not exposed               | 32    | 43       | 1.00                        |
| Suspected                 | 26    | 21       | 1.66                        |
| Exposed                   | 38    | 22       | 2.54*                       |
|                          |       |          | Extended Mantel test p < 0.01 |

*0.05 > p > 0.01.
*p < 0.01 (Mantel-Haenszel test).

Table 6. Age-adjusted lung cancer risk associated with smoking and asbestos exposure in Yokosuka, Japan.

| Histology (Kreyberg)       | Smoking* | Asbestos exposure | Age- | asbestos-adjusted | Age- | asbestos-adjusted |
|----------------------------|----------|-------------------|------|-------------------|------|-------------------|
|                            |          | Not exposed       | Suspected |                  |                  |                  |
| I + II                     |          | 1.00              | 2.33 | -                 | 1.00 | 6.01*             |
| Smokers                    |          | 3.38              | 4.84 | 8.28*             | 2.81* |
|                            |          | (1.00)            | (1.56)| (2.81)*           |       |
| Age- and smoking-adjusted |          | 1.00              | 1.56 | 2.41*             |       |
| I                          |          | 1.00              |      | 1.00              |      | 13.51*            |
| Smokers                    |          | (1.00)            | (1.94)| (3.22)*           |       |
|                            |          | 1.00              | 1.94 | 3.40*             |       |
| Age- and smoking-adjusted |          |                  |      |                  |      |                  |
| II                         |          | 1.00              | 2.33 | 0.74              | 1.00 |                  |
| Smokers                    |          | 1.60              | 1.93 | 2.25              | 1.54 |                  |
|                            |          | (1.00)            | (1.16)| (1.72)            |       |
| Age- and smoking-adjusted |          | 1.00              | 1.16 | 1.72              |       |

*Non-smokers includes ex-smokers who had quit smoking for 10 years or more.
Those who had refrained from smoking less than 10 years are included in smokers.
*Dash indicates not applicable because of zero division in odds ratio calculation.
*0.05 > p > 0.01, Mantel-Haenszel test.
'0.05 > p > 0.01, extended Mantel test.
'p < 0.01, extended Mantel test.

...significant increasing risk [p < 0.05] according to exposure level, while only a mild elevation of no statistical significance was noted for group II.

**Discussion**

Yokosuka City has long attracted asbestos researchers' interest because of the high mortality for lung cancer, high prevalence of asbestososis, pleural plaques, and asbestos bodies, as well as the high incidence of malignant mesothelioma (16). Age- and smoking-adjusted relative risks of 2.41 (p < 0.05) and 1.56 associated with asbestos exposure and suspected exposure, respectively, were shown in this study. This relative risk of 2.41 is lower than the relative risks of 2.71 to 11.7 previously reported in asbestos workers (17–21) and was more comparable to the relative risks of 1.7 to 4.75 among shipyard workers (1,4,22,23), consistent with the fact that most of the lung cancer cases exposed to asbestos had worked in the shipyards or the Imperial naval factory.

The histologic type of lung cancer among asbestos-exposed workers has been a matter of interest (6–9) and has been reviewed by Churg (10), who concluded that all histological types of lung cancer occurred almost evenly in these workers. It is known, however, that autopsied cases and surgical specimens show different distributions of histologic types of lung cancer; adenocarcinoma is more common among autopsied cases than surgical specimens (9). Thus, the distribution of histologic types of lung cancer among asbestos-exposed workers based only on autopsied cases tended to show a higher percentage of adenocarcinoma than among non-exposed populations (7), while the distribution based on surgical specimens as well as autopsied cases showed a lower proportion of adenocarcinoma (9). In the present study, the elevated lung cancer risk associated with asbestos exposure was demonstrated only for the histologic type of Kreyberg group I, but not for group II, which included adenocarcinoma, after controlling for age and smoking history. This result may not conflict with the previous studies, as 30% of the histologic diagnoses of the cases in this study were based on specimens used in cytological diagnosis and obtained at surgical operations. Our results were also consistent with an epidemiological study in which elevated lung cancer risk associated with potential exposure to asbestos was observed only for squamous cell carcinoma after adjusting for age and cigarette smoking (5). A large-scale epidemiological study may be necessary for a more detailed analysis of cell type, since histological cell types were grouped into only two categories because of the limited number of lung cancer cases in this study.

Doll et al. (24) reported a close relationship between the amount of daily smoking and the development of Kreyberg type I lung cancer among males, but only a slight association with other histological types, e.g., adenocarcinoma. Koo et al. (25) and Segi et al. (26) have also shown similar relationships among males.

Recent studies, however, showed an elevated risk of adenocarcinoma of the lung due to smoking (27–33). According to these reports, the relative risk of adenocarcinoma ranges from 1.3 to 3.1 (27–33) lower than the range of 1.8 to 11.8 for squamous cell carcinoma (27–33); 3.9 to 13.8 for small cell carcinoma (27–32); and 3.4 to 7.3 for large cell carcinoma (28,30–32). These levels of lung cancer risk suggest that the relative risk of 1.64 for Kreyberg group II lung cancer obtained in the present study, although not statistically significant, may be within the range of relative risk for adenocarcinoma and is still lower than the relative risk for Kreyberg group I lung cancer. The sample size was limited since the main purpose of the study was to demonstrate the association of asbestos exposure with lung cancer. The small sample size may be responsible for the...
nonsignificance of the relative risk.

Interviews were conducted without knowing whether a subject was an actual case or a control, thus, there was no influence on the questioning and recording done by the interviewer.

Obviously, occupational and smoking history could not be obtained directly from the deceased patients, and these data were obtained from families some years after the patients' deaths. Family recall might have been incomplete or imprecise, particularly with regard to the amount of smoking and attempts to stop or resumption of smoking, and this might be a possible reason why unexpected results were observed on the relative risks for exsmokers and amounts of smoking in this study. On the other hand, the simpler question of whether the subject had smoked or had not smoked must have been answered correctly, thus assuring reasonable result.

The level of asbestos exposure was estimated on the basis of detailed occupation history. Occupation and work site were used as an indirect indicator of asbestos exposure, and answers to these seemingly neutral questions should not have introduced biases in answers. The exposure level might be underestimated if recall was grossly insufficient. Such cases, however, were seldom encountered in this study.

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