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Investigations into Malignant Neoplasms Complicated by Silicosis

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Fifty patients (25.6%) developed malignant neoplasm among 195 dead silicosis patients during the 10-year period from 1975 until 1984. Silicosis patients showed a significantly higher incidence of lung cancer and malignant lymphoma in comparison with the general male population of Oita Prefecture and Japan. Lung cancer was chiefly occured in Type III (PR3) silicosis. The most prevarent histological type was squamons cell carcinoma and adenocarcinoma was very few. Tumors were mainly found in right lower lobe and the peripheral type had a somewhat higher incidence than hilar type. The patients with malignant lymphoma, all of them were non Hodgkin's lymphoma, died at a younger age than the patients with lung cancer. The reason for the high incidence of lung cancer in silicosis is attributed to the pneumoconiotic chronic inflammatory granulation tissue or the scar tissue giving rise to abnormal proliferation in the bronchial epithelium. Moreover it was conceivable that insufficient T-lymphocyte function in silicosis patients may facilitate the development of malignant neoplasms and especially malignant lymphoma.

Key Words : Malignant neoplasm, Lung cancer, Malignant lymphoma, Silicosis, Pneumoconiosis

INTRODUCTION

In recent years, the incidence of malignant neoplasms has increased dramatically, and the seriousness of the situation can be inferred from the fact that, since 1981, this has

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been primary cause of death in Japan. The reason for this rise in the incidence of malignant neoplasms, has been attributed to environmental contamination including exhaust gases, atmospheric pollution, and the spreading use of oil and oil-based products. It is also generally recongnized that metals, such as chromium, nickel, and arsenic, as well as asbest and radioactive substances, are occupational carcinogens. While medical opinion agrees that general dusts, including silica, do not have a cancerogenic action, recent evidence suggests that there is a high incidence of lung cancer associated with silicosis[1~4].

The authors have also found and reported that tunnel diggers with silicosis present a high incidence of lung cancer[5]. The present report refers to our studies of malignant neoplasms complicated by silicosis.

MATERIALS AND METHODS

During the 10-year period from 1975 until 1984, 1445 patients were diagnosed and treated for silicosis. Of these, 195 died, of whom 50 (25.6%) developed malignant neoplasm

Table 1. Malignant Neoplasms Associated With Silicosis

Malignant neoplasms	No. of cases	%
Lung	17*	8.7
Stomach	10*	5.1
Liver	8	4.1
Colon & Rectum	4	2.1
Lymphoma	4	2.1
Esophagus	1	0.5
Bile duct	2*	1.0
Pancreas	2	1.0
Kidney	1*	0.5
Bladder	—	—
Head	1	0.5
Leukemia	1	0.5
Myeloma	1	0.5
Thymoma	1	0.5
Sarcoma	1	0.5
Total	50(54*)	25.6

* double cancer

as a complication (Table 1). Of these 50 patients, four had double cancer, i.e., two had lung cancer and gastric cancer, one had lung cancer and renal cancer, and one had gastric cancer and cancer of the bile duct. The total of 54 malignant neoplasms included 17 lung cancers, thus accounting for the major share, followed by 10 gastric cancers, eight hepatomas, four colonic cancers, and four malignant lymphomas.

Except for one patient, all fatal cases of silicosis encountered by the author were men, a fact that prompted us to study the incidence of malignant neoplasm complicated by silicosis by statistical comparison with the incidence of malignant neoplasm in men in general throughout Japan and for the prefecture of Oita (Kyushu Island).

RESULTS

1. Incidence of malignant neoplasm in men in general throughout Japan (Table 2)

According to the 1982 statistics compiled by the Ministry of Health and Welfare to assess the movement of the nation's population, the incidence of malignant neoplasm in men general throughout Japan was 26.5%. The breakdown was given as : 7.8% for gastric cancer, the group accounting for the largest share, followed by 4.6% for lung cancer, 2.9% for hepatoma, and 2.2% for colonic cancer, while malignant lymphoma showed a low incidence of 0.1%. Comparison of the incidence of silicosis with the incidence of malignant neoplasms in the male population in general on the basis of the chi-square test indicated that the former had a significantly higher incidence of lung cancer and malignant lymphoma.

2. Incidence of malignant neoplasm in men in general in Oita Prefecture (Table 3)

According to the evidence of the 1982 Yearbook of Public Health and Hygiene of Oita Prefecture, the incidence of malignant neoplasms in men in general in the prefecture is given as 24.5%. Again, similar to the national statistics, gastric cancer accounted for the largest share of 6.6%, followed by lung cancer with 4.5%, hepatoma with 3.2%, and colonic cancer with 2.1%, while malignant lymphoma showed the lowest frequency amounting to 0.1%. The results of the chi-square test suggest that there is no significant difference in the incidence of malignant neoplasms between the general patient population of Oita Prefecture and that of the country as a whole. It was again found that silicosis

Table 2. Malignant Neoplasms in Japan

Malignant neoplasms	Code of ICD	No. of cases	Incidence (%)
Lung	162	17,555	4.6*
Stomach	151	30,036	7.8
Liver	155	11,278	2.9
Cclon & Rectum	153, 154	8,625	2.2
Lymphoma	200, 201	310	0.1**
Bile duct	156	3,148	0.8
Pancreas	157	5,033	1.3
Esophagus	150	4,646	1.2
Kidney	189	1,214	0.3
Leukemia	204−208	2,789	0.7
Myeloma	203	706	0.2
Others			
Total		102,242	26.5

* $p<0.01$ ** $p<0.001$

Table 3. Malignant Neoplasms in Oita Prefecture

Malignant neoplasms	Code of ICD	No. of cases	Incidence (%)
Lung	162	225	4.5*
Stomach	151	330	6.6
Liver	155	159	3.2
Colon & Rectum	153, 154	102	2.1
Lymphoma	200, 201	4	0.1**
Bile duct	156	35	0.7
Pancreas	157	50	1.0
Esophagus	150	36	0.7
Kidney	189	21	0.4
Leukemia	204−208	28	0.6
Myeloma	203	6	0.1
Others			
Total		1,215	24.5

* $p<0.01$ ** $p<0.001$

patients showed a significantly higher incidence of lung cancer and malignant lymphoma in comparison with the general male population of Oita Prefecture.

3. Lung cancer complicated by silicosis (Table 4)

Table 4. Lung Cancer Associated With Silicosis

	Range	Mean
Age at diagnosis (years)	47–75	62.2
Age at death (years)	48–75	63.3
Exposure period (years)	5–38	15.8
Category of profusion		
1	2	8.7%
2	7	30.4%
3	10	43.5%
4	4	17.4%

Table 5. Histologic Features of Lung Cancer

	Hilar	Peri-pheral	Total	(%)
Sguamous cell carcinoma	6	7	13	(54.2)
Small cell carcinoma	3	2	5	(20.8)
Large Cell carcinoma	1	3	4	(16.7)
Adenocarcinoma	0	1	1	(4.2)
Adenosquamous carcinoma	0	1	1	(4.2)
Total	10	14	24	(100.0)

Table 6. Location of Lung Cancer

	Hilar	Peri-pheral	Total	(%)
Right upper lobe	3	1	4	(16.7)
middle lobe	1	0	1	(4.2)
lower lobe	2	7	9	(37.5)
Left upper lobe	4	2	6	(25.0)
lower lobe	0	4	4	(16.7)
Total	10	14	24	(100.0)

We investigated the significance of silicosis as a complication of lung cancer for the 17 deceased and the six surviving patients. The patients' ages at the time of diagnosis of lung cancer ranged from 47 through 75 years, averaging 62.2. Their ages at death ranged from 48 through 75, averaging 63.3. The duration of exposure to dusts varied from five to 38 years, averaging 15.8 years, and the types of silicosis indicated on the X-rays were Type I (PR 1) in two patients (8.7%), Type II (PR 2) in seven patients (30.4%), Type III (PR 3) in 10 patients (43.5%) and Type IV (PR 4) in four patients (17.4%). Type III (PR 3) of the disease was, thus, the most common.

In one patient, double cancer had developed, with peripheral type squamous cell carcinoma of the left S^6 and hilar type squamous cell carcinoma of the right upper bronchus. A clinical and histopathological examination was performed on a total of 24 lung cancers. Histological evidence showed that squamous cell carcinoma was the most prevalent, manifesting itself in 13 of the 24 tumors (54.2%), followed by small cell carcinoma in five (20.8%) and large cell carcinoma in four (16.7%). Adenocarcinoma was the rarest cancer, occurring in only one (4.2%). Adenosquamous carcinoma was detected in one (4.2%) (Table 5). Hilar type cancer developing from the segmental bronchi to the center was discovered in 10, and peripheral type cancer spreading from the subsegmental bronchi to the periphery occurred in 14. This indicates that the peripheral type had a somewhat higher incidence. Squamous cell carcinoma and small cell carcinoma were found to occur roughly at the same incidence in the hilar and peripheral types. However, large cell carcinoma, adenocarcinoma, and adenosquamous carcinoma occurred largely in the peripheral type.

The breakdown by the location of the disease shows a prevalence of the right lower lobe with nine (37.5%), followed by the left upper lobe in six (25.0%), the right upper lobe and left lower lobe in four (16.7%), and the middle lobe in one (14.2%) (Table 6).

4. Malignant lymphoma complicated by silicosis (Table 7)

Malignant lymphoma occurred in four patients, all of whom had non-Hodgkin's lymphoma. Their ages at the time of diagnosis ranged from 43 through 53 years, averaging 48.3. Their ages at death ranged from 47 through 58 years, averaging 53.0 years. Compared with the patients having lung cancer as a complication, they died at a younger age. The duration of exposure to dust varied from five to 23 years, averaging 12.8 years. The types of silicosis on the X-rays were Type I (PR 1) in one patient, Type II (PR 2) in

Table 7. Malignant Lymphoma Associated With Silicosis

	Range	Mean
Age at diagnosis (years)	43–53	48.3
Age at death (years)	47–58	53.0
Exposure period (years)	5–23	12.8
Category of profusion		
1	1	25.0%
2	1	25.0%
3	2	50.0%

one patient, and Type III (PR 3) in two patients.

DISCUSSION

As a result of the significant progress achieved in general therapeutics and medical technology as well as the development of strong antibitiocs and antituberculosis drugs, silicosis patients who would formerly have died at a young age from pulmonary tuberculosis, pneumonia, secondary bronchitis, and other lung infections and pulmonary insufficiencies, have had their average life expectancy increased. There has been a rise in the incidence of malignant neoplasm, which used to be rare. Thus, we have studied the relationship between silicosis and malignant neoplasm.

Since ROSTOSKI[6] published his "Schneeberger Lungenkrebs" in 1926, there have many reported in the literature. A large number of them cite a high incidence of lung cancer in silicosis patients on the overall evidence of autopsy results[1~3]. The evidence of many epidemiological investigations indicates, though, that the relationship between the two conditions must be denied[7~9]. In Japan, however, evidence has been obtained chiefly from autopsy results since the publication of the report by TAKEDA *et al.*[10] in 1964, suggesting that there is a causal relationship between the two.

The reason for the high incidence of lung cancer in silicosis is attributed to the pneumoconiotic chronic inflammatory granulation tissue or the scar tissue giving rise to abnormal proliferation in the bronchial epithelium. It is, therefore, assumed that either scar cancer in the ordinary sense of the term occurs or that the pneumoconiotic granulation

tissue may locally coexist with some carcinogenic substance absorbed, for some reason, at the same time[11].

SUZUKI *et al.*[4] have stated that, except for asbest workers, no difference can be found by occupation. By contrast, YASUDA *et al.*[12] discovered a significant difference, reporting that the incidence of lung cancer is significantly higher by as much as 4.3 times for silicosis-affiliated workers in the metal mining industry as compared with ordinary subjects. Their findings also indicate that no significant difference is detectable for coal miners with silicosis so that to account for the higher incidence of lung cancer among metal miners than coal miners, it is likely that some carinogenic factor other than silicon dioxide (silica) may be operative (for example, radioactive substances, arsenic or chromium). The subjects studied by the ourselves were tunnel diggers with silicosis who were found to present an incidence of lung cancer significantly above that of the ordinary male population. It will be necessary to carry out further research to determine whether there are significant occupation-related differences in the incidence of lung cancer for silicosis patients and to clarify the mechainsm by which cancer forms.

There are virtually no reports claiming a significantly higher incidence of malignant lymphoma for silicosis patients. ENTERLINE[13] conducted a survey of coal miners throughout the United States and found that the standardized mortality ratio (SMR) for lymphosarcoma and leukemia was 1.68 and 1.50, respectively, the incidence being a high one. It is general knowledge that silicosis patients exhibit a loss in macrophage function[14], a drop in cellular immunity[15], and progressive disorders of the humoral immunity system[16][17].

Immunocompromised patients with insufficient T-lymphocyte function are generally subject to a higher incidence of malignant neoplasms and especially malignant lymphoma[18][19]. Loss of T-lymphocyte function results in the breakdown of the macrophage system and reduces interferon production so that the patient's resistance to virus attacks is diminished, a condition which may well facilitate the development of malignant lymphoma[20].

Apart from lung cancer and malignant lymphoma, the patients encountered by the authors did not present with malignant tumors developing at a significantly higher incidence in silicosis patients. However, some reports are available suggesting that, in silicosis patients, there is a high incidence of carcinoma of the digestive organs including gastric cancer, and cancer of the urinary tract including renal cancer and cancer of the bladder. The task for the future will be to widen the scope of research to include not only the direct carcinogenic action of silica and other dusts, but also immunological disorders affecting the

body as a whole.

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