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Lung Cancer in Patients with Idiopathic Pulmonary Fibrosis

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NAGAI, A., CHIYOTANI, A. and KONNO, K. *Lung Cancer in Patients with Idiopathic Pulmonary Fibrosis.* Tohoku J. Exp. Med., 1992, **167** (3), 231-237 —— We investigated lung cancer in 99 patients with idiopathic pulmonary fibrosis (IPF). Lung cancer was found in 31 (31.3%) of 99 patients with IPF. Most (87.9%) tumors, including squamous cell carcinoma, were observed in the peripheral region of the lung, whereas the distribution of histologic types of cancers was similar to that seen in ordinary lung cancer. Peripheral tumors were frequently seen in the lower lobe, where fibrotic shadow was prominent. However, the severity of fibrosis was not related with the prevalence or histologic type of lung cancer. Two-thirds of IPF patients having a smoking history of over 40 years developed lung cancer. When compared with nonsmoking IPF control subjects, the relative risk of smoking in IPF patients was 3.5, identical with that reported for smokers in the general population. We suggest that smoking in patients with IPF is an additive risk factor for the development of lung cancer. We also speculate that the high prevalence of peripheral squamous cell carcinoma might be associated with cigarette smoking. ———— lung cancer; smoking; idiopathic pulmonary fibrosis

It has been reported that diffuse interstitial pulmonary fibrosis is associated with lung cancer (Callahan et al. 1952; Spain 1957; Meyer and Liebow 1965; Turner-Warwick et al. 1980a), and the prevalence of lung cancer in patients with pulmonary fibrosis ranges from 4.4% (Tukiainen et al. 1983) to 40.4% (Matsuoka and Kira 1983). However, most previous reports have included pulmonary fibrosis associated with known causes, and the association between lung cancer and idiopathic pulmonary fibrosis (IPF) has not been fully investigated. The subjects of this investigation were patients with idiopathic pulmonary fibrosis. It seems reasonable to confine the analysis to this single definable disease entity and exclude other causes of interstitial lung disease such as collagen diseases, sarcoidosis and infectious diseases. This study attempted to determine whether there is an association between lung cancer and the severity of fibrosis, whether

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there is any characteristic feature in the histologic type or location of lung cancer in patients with IPF, and whether smoking is a risk factor for the development of lung cancer in these patients. We investigated 99 patients with IPF who were diagnosed and followed at Tokyo Women's Medical College during the past 12 years.

Materials and Methods

One hundred fifty-four patients with diffuse pulmonary fibrosis were examined in our hospital during the 12-year period. Using established criteria of diffuse interstitial lung disease of unknown cause (Crystal et al. 1976; Turner-Warwick et al. 1980b), a diagnosis of IPF was made in 99 patients from all the findings of chest radiography, lung biopsy (3 or 4 transbronchial lung biopsied specimens), bronchoalveolar lavage, serum immunological examinations and pulmonary function tests as well as detailed historical evaluation. Patients with radiation pneumonitis, fibrosis appearing in survivors of lung cancer, or known origin fibrosis such as collagen disease, sarcoidosis, hypersensitivity pneumonitis and pneumoconiosis were excluded from the study. Smoking history was obtained from the patients according to the modified BMRC questionnaire (Medical Research Council 1960). The severity of pulmonary fibrosis was determined by chest radiographs according to the stage of diffuse pulmonary fibrosis (Lillington and Jamplis 1977). Briefly, ground glass or small nodular shadow was assessed as early stage, reticular shadow as intermediate, and honeycomb appearance as advanced stage. Histologic examination for lung cancer was performed on specimens obtained by transbronchial lung biopsy (27 patients), surgical treatment (3 patients) or autopsy (1 patient). To determine risk factors for smoking, IPF male patients between the ages of 55 and 80 were entered into an age-matched study. The prevalence of lung cancer, smoking histories and severity of pulmonary fibrosis were compared using Student's t-test, chi-square test, or Fisher's exact test. $p<0.05$ was accepted as significant.

Results

Lung cancer occurred in 31 (31.3%; 27 men and 4 women) of 99 patients (67 men, 67.7%; 32 women, 32.3%) with IPF. There was no difference in mean age between IPF patients with (70.9±7.9 [mean±S.D.]) and without (68.6±7.9) lung cancer. Among 27 IPF patients with peripheral lung cancer, the severity of pulmonary fibrosis classified according to the appearance of chest radiographs was early stage in 10 (37.0%) patients, intermediate stage in 11 (40.7%) and advanced stage in 6 (22.2%).

Table 1. *Cell types of lung cancer in patients with idiopathic pulmonary fibrosis*

Cell types	Number of patients (%)	Central region	Peripheral region
Squamous cell carcinoma	14 (45.2%)	1	13
Adenocarcinoma	10 (32.3%)	0	10
Small cell carcinoma	4 (12.9%)	2	2
Large cell carcinoma	2 (6.5%)	1	1
Adenosquamous cell carcinoma	1 (3.2%)	0	1

TABLE 2. *Severity of radiographical fibrosis and cell type of peripheral lung cancer*

	Cell type				
	Squamous	Adeno	Small	Large	Adenosquamous
Early stage[a]	6[b]	3	1		
Intermediate stage	3	6		1	1
Advanced stage	4	1	1		

[a]Early stage: ground glass or small nodular shadow; intermediate stage: reticular shadow; advanced stage: ring shadow (honeycomb appearance).
[b]The data represent numbers of patients.

Table 1 shows the distribution of histologic types of lung cancer. Half of the 31 carcinomas were squamous cell carcinoma, one-third were adenocarcinoma, and about one-tenth were small cell carcinoma. The distribution of cell types was similar to that of lung cancer in ordinary bronchogenic carcinoma in Japan (Yoshimura and Yamashita 1982). Table 2 shows the severity of pulmonary fibrosis and histologic cell types of peripheral lung cancer. The histologic types and prevalence rates of cancer were not related ($p=0.346$) to the radiographic stage of pulmonary fibrosis.

The location of lung cancers is shown in Tables 1 and 3. It is clear that more tumors were found in the peripheral regions of the lungs than in the central region. Thirteen of 14 squamous cell carcinomas and all adenocarcinomas were seen in the periphery of the lungs. The peripheral tumors were more frequently found in the lower part (lobe) of the lung, where fibrotic shadow was more prominent, than in the upper part.

Table 4 compares the prevalence of lung cancer between smokers (current and ex-smokers) and non-smokers with IPF. Smokers with IPF had a significantly ($p<0.05$) higher prevalence than non-smokers. To determine the risk factor smoking presents in the development of lung cancer in patients with IPF, smoking histories in age-matched male fibrotic patients with or without lung cancer were

TABLE 3. *Location of lung cancer*

Location	Number of patients
Central regions of the lung	4 (12.9%)
Periphery of the lung	27 (87.1%)
right upper lobe	5
right middle lobe	1
right lower lobe	11
left upper lobe	2
left lower lobe	8

TABLE 4. *Smoking history in patients with lung cancer and idiopathic pulmonary fibrosis (IPF)*

	Patients with IPF			
	Smoker	Non-smoker	Unknown[a]	Total
+Lung cancer	27 (male, 26 female, 1)	3 (male, 1 female, 2)	1 (female)	31
−Lung cancer	44	25	—	69
Total	71	28	1	100

[a]Smoking history was not precisely determined. This patient was excluded from smoker or non-smoker group.

TABLE 5. *Relationship of smoking history with lung cancer in age-matched male smokers with idiopathic pulmonary fibrosis*

	Lung cancer present	Lung cancer absent	*t*-test
No. of patients	25	22	N.S.[a]
Age (years)	72.3±5.9[b]	69.7±6.4	N.S.
B.I.[c]	1024.7±498.1	1056.4±621.6	N.S.
Cigarettes/day	25.5±14.6	28.6±14.9	N.S.
Smoking period (years)	44.4±10.9	38.5±11.9	N.S.
Current/(current+ex)[d]	76%	18%	

[a]N.S., not significant.

[b]Mean±S.D.

[c]B.I., Brinkman index (=cigarette number per day×smoking period in years).

[d]Current/current+ex, ratio (%) of number of current smokers to all smokers (current+ex−smokers).

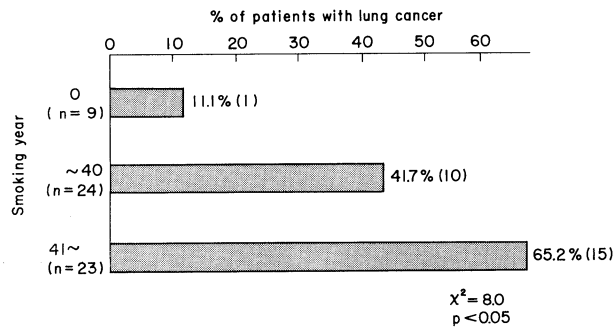

Fig. 1. Relationship between smoking duration (years) and prevalence rates of lung cancer in male IPF patients including the age-matched male smokers in Table 5. The prevalence rate is significantly higher in patients whose smoking histories were longer than 40 years compared with patients having a shorter smoking history. Numbers within parentheses are numbers of patients with lung cancer.

compared. As shown in Table 5, there was no difference in smoking history, including Brinkman index (=cigarettes per day×smoking years) and cigarettes smoked per day. Smoking duration (years) was longer in patients with lung cancer than in those without cancer, but the difference was not significant ($p<0.1$). Most IPF patients with lung cancer were current smokers. When smoking duration was classified into 3 groups (0 years, less than or equal to 40 years, more than 40 years) (Fig. 1), IPF patients having a smoking history of more than 40 years showed a strikingly high prevalence rate of lung cancer, whereas only one of 9 non-smokers with IPF had lung cancer.

Discussion

This study demonstrated that lung cancer frequently occurs in patients with IPF, that most tumors (87.9%) were located at the periphery of the lower part of the lung, and that the prevalence of the cancers was not related to the radiographic stage (severity) of pulmonary fibrosis. Smokers with IPF were at relatively greater risk for lung cancer, and this risk increased with increased duration of smoking.

The excess cancer risk in relation to smoking in patients with pulmonary fibrosis is controversial. Meyer and Liebow (1965) found that all patients with both lung cancer and pulmonary fibrosis were smokers, and subsequently Turner-Warwick and coworkers pointed out that a substantial proportion of patients with both lung cancer and pulmonary fibrosis were smokers (Turner-Warwick et al. 1980a). However, others found no difference in smoking history between fibrotic patients with or without lung cancer (Kawano et al. 1983 ; Okano et al. 1989). It is likely that these differing results are related to the details of smoking history. In comparing fibrotic patients with or without lung cancer, our study found no difference in smoking history between them. But when components of smoking history in age-matched male smokers with IPF were compared, two-thirds of IPF patients having a smoking history of more than 40 years had lung cancer (Fig. 1). The prevalence rates of coexistent lung cancer in patients having a smoking history of less than 40 years or no history of smoking were 41.7% and 11.1%, respectively. With regard to the Brinkman index and cigarettes smoked per day, the prevalence of lung cancer was not related with the number of cigarettes smoked. As described above, the prevalence of lung cancer in smokers with IPF was significantly increased compared with that in non-smokers. These findings suggest that smoking produces excess cancer risk in patients with IPF and the duration of smoking may be closely associated with the development of lung cancer.

In our study, lung cancer was found in 10.7% of nonsmokers with IPF and in 38.0% of smokers with IPF. Compared with nonsmoking IPF control subjects, the relative risk of cigarette smoking for lung cancer in IPF patients was about 3.5. The relative risk of smoking in our study was similar to that of

smokers in the general population study by Shimizu et al. (1986). Therefore, we suggest that cigarette smoking in IPF patients acts as an additive risk factor for the development of lung cancer. In other words, cigarette smoking and IPF are regarded as independent factors associated with the development of lung cancer.

The interrelation of the development of pulmonary fibrosis and lung cancer in smokers is difficult to interpret. Although we could not determine exactly when pulmonary fibrosis started, the history of fibrosis in most patients is likely to have been 10 years at most, as suggested by their clinical history. The history of smoking in most fibrotic patients with lung cancer was more than 10 years, and much longer than the history of fibrosis. One simple explanation for the increased coexistence of lung cancer in smokers with IPF is that the excess cancer risk in smokers with IPF may be due to a summation of the effects of these two independent pathogenetic factors (smoking and fibrosis). As previously described, both smoking and fibrosis are associated with lung cancer, and in the development of lung cancer, fibrosis appears to act independently of cigarette smoking. These findings are quite different from pulmonary asbestosis, which shows a marked multiplicative effect when combined with cigarette smoke (Hammond et al. 1979).

In this study, one-third of IPF patients had lung cancer. The prevalence rate of cancer was slightly higher than those given in other reports. An explanation for the different results may be a difference in patient profile, i.e., the length of smoking history and whether the report analyzed a single definable disease, since we examined only IPF patients and excluded other cases of interstitial lung disease. Another explanation might be referral bias, e.g., more ill patients with fibrosis, including those with lung cancer, may have been likely to be referred, although these factors apply to some extent to previously reported cases as well.

It is interesting that in smokers with IPF squamous cell carcinoma was frequently found in the peripheral region of the lung (13 of 14 squamous cell carcinomas). Cigarette smoking is well known to be associated with squamous cell carcinoma, and squamous cell carcinoma occurs mainly in the large bronchi. Spencer reported that the majority of scar cancers were adenocarcinoma, but a few squamous cell carcinomas may originate in this manner (Spencer and Liebow 1977). However, Churg has recently reported that all of the common histologic types of lung cancer are related to cigarette smoking (Churg 1988). Taking into account our finding that the distribution of the histologic types of lung cancer in IPF patients was similar to that of patients with ordinary bronchogenic carcinoma, coexistent peripheral lung cancer in IPF may result from uncontrolled epithelial proliferation secondary to fibrosis and chronic inflammation, as has been previously pointed out by Spain (1957). Cigarette smoking may provide an additive effect for the development of peripheral lung cancer.

References

1) Callahan, W.P., Sutherland, J.C., Fulton, J.K. & Kline, J.R. (1952) Acute diffuse interstitial fibrosis of the lungs. *Arch. lntern. Med.*, **90**, 468-482.
2) Crystal, R.G., Fulmer, J.D., Roberts, W.C., Moss, M.L., Line, B.R. & Reynolds, H.Y. (1976) ldiopathic pulmonary fibrosis : Clinical, histologic, radiographic, physiologic, scintigraphic, cytologic, and biochemical aspects. *Ann. Intern. Med.*, **85**, 769-788.
3) Churg, A. (1988) Tumors of the lung. In : *Pathology of the Lung*, edited by W.M. Thurlbeck, Thieme Medical Publishers, New York, pp. 311-424.
4) Hammond, E.C., Selikoff, I.J. & Seidman, H. (1979) Asbestos exposure, cigarette smoking and death rates. *Ann. NY Acad. Sci.*, **330**, 473-490.
5) Kawano, O., Takami, T., Amitsuna, T., Ohnari, K., Yamakido, M. & Nishimoto, Y. (1983) Clinical studies of idiopathic interstitial pneumonia associated with lung cancer. *J. Jpn. Soc. Intern. Med.*, **72**, 1731-1739.
6) Lillington, G.A. & Jamplis, R.W. (1977) Diffuse interstitial, micronodular and mixed patterns. In : *A diagnostic Approach to Chest Diseases*, 2nd ed. Williams and Wilkins Company, Baltimore, pp. 33.
7) Matsuoka, R. & Kira, E. (1983) Smoking, air-pollution, occupation, IIP, and lung cancer. *Intern. Med.*, **52**, 614-619. (in Japanese)
8) Medical Research Council (1960) Standardized questionnaire on respiratory symptoms. *Br. Med. J.*, **2**, 1655.
9) Meyer, E.C. & Liebow, A.A. (1965) Relationships of interstitial pneumonia, honeycombing and atypical epithelial proliferation to cancer of the lung. *Cancer*, **18**, 322-351.
10) Okano, H., Tanimoto, H. & Nakata, K. (1989) Lung cancer associated with idiopathic interstitial pneumonia. *Jpn. J. Chest Dis.*, **48**, 189-198.
11) Shimizu, H., et al. (1986) Risk of lung cancer by histologic type among smokers in Miyagi Prefecture. *Jpn. J. Clin. Oncol.*, **16**, 117-121.
12) Spain, D.M. (1957) The association of terminal bronchiolar carcinoma with chronic interstitial inflammation and fibrosis of the lungs. *Am. Rev. Tuberc.*, **76**, 559-567.
13) Spencer, H. & Liebow, A.A. (1977) *Pathology of the Lung.* 3rd ed., Pergamon Press, Oxford.
13) Tukiainen, P., Taskinen, E., Holstl, P., Kohola, O. & Valle, M. (1983) Prognosis of cryptogenic fibrosing alveolitis. *Thorax*, **38**, 349-355.
15) Turner-Warwick, M., Lebowitz, M., Burrows, B. & Johnson, A. (1980a) Cryptogenic fibrosing alveolitis and lung cancer. *Thorax*, **35**, 496-499.
16) Turner-Warwick, M., Burrows, B. & Johnson, A. (1980b) Cryptogenic fibrosing alveolitis : Clinical features and their influence on survival. *Thorax*, **35**, 171-180.
17) Yoshimura, K. & Yamashita, N. (1982) Clinical statistical observation of 4931 cases with lung cancer by histological types ; results of field study in Japan. *Lung Cancer*, **22**, 1-16.