A number of studies have shown a high incidence of lung cancer in patients with idiopathic pulmonary fibrosis (9.8 to 38%) compared to control subjects (2 to 6.4%). A similar trend occurs in other entities that affect the interstitial lung compartment, such as systemic sclerosis and sarcoidosis, as well as occupational diseases. The pathogenesis of lung cancer in patients with diffuse pulmonary fibrosis is still unclear. Recent progress in molecular and cellular biology has shed some light on the possible interactions of several types of inflammatory cells, following the deleterious effects of toxic factors leading to alveolitis, and destruction and disorganization of lung parenchyma, which results in fibrosis. Further research in the field would enhance our understanding of the pathogenic mechanisms of cancer development in these patients, and to explain the reason for the different incidence of lung cancer in patients with various interstitial lung diseases.

Key words: asbestosis; cancer; lung cancer; malignancy; pulmonary fibrosis; sarcoidosis; scar cancer

Abbreviations: CFA = cryptogenic fibrosing alveolitis; CI = confidence interval; IL = interleukin; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; NK = natural killer; RA = rheumatoid arthritis; RR = relative risk; SIR = standardized incidence ratio; SLE = systemic lupus erythematosus; UIP = usual interstitial pneumonitis

An excessive relative risk (RR) [range, 2 to 14] of lung cancer has been found in patients with pulmonary fibrosis of diverse etiology compared to the general population. Although the pathogenesis of cancer in such cases is still obscure, it appears that cases without fibrosis may also have an excessive incidence, but to a much lesser extent. If this is so, it raises fundamental questions about the relationship between exuberant collagen deposition in the lung and neoplastic change. In this article, we review the existing data on the pathogenesis and incidence of lung cancer in patients with several forms of interstitial lung disease (ILD), as well as in patients with local fibrosis, the so-called “scar cancer.”

Pathogenesis of Lung Cancer in Patients With ILDs

Many reports have documented an association between lung cancer and diffuse pulmonary fibrosis. These carcinomas are located mainly in the lower lobes, and their histologic type is similar to that in patients without fibrosis. Squamous cell carcinoma seems to be the most common, although an increased frequency of adenocarcinoma, including bronchioalveolar cell carcinoma and small cell carcinoma, has been reported. Areas of atypical epithelial proliferation were seen in the terminal airspaces in eight patients with idiopathic diffuse pulmonary fibrosis; in three of these patients, cancer developed within areas of advanced fibrosis.

The precise properties of fibrosis that lead to the development of carcinoma are unknown. One possibility that has been suggested is that scarring causes lymphatic obstruction, resulting in a local increase in potentially carcinogenic material. High concentrations of carcinoembryonic antigen in the BAL fluid of patients with fibrosing alveolitis, particularly in patients with associated lung cancer, have also been reported. Such high levels of carcinoembryonic antigen may be a marker of premalignant metaplasia and hyperplasia, and may reflect a greater risk of pulmonary carcinoma in the clinical course of pulmonary fibrosis. Moreover, in patients with cryptogenic fibrosing alveolitis (CFA), hyperplasia of alveolar lining cells has been observed, which may lead

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to an increased incidence of alveolar cell carcinoma. The fundamental reason for predisposition to neoplastic change is largely unknown, although alterations in the function of cells controlling the inflammatory response must be considered. If defective surveillance mechanisms are important, the finding of autoantibodies in a high proportion of patients with CFA is of interest. A reduction of normal delayed hypersensitivity responses in patients with lung cancer has been used as further evidence of a surveillance defect. However, the delayed skin type reactions are not in general reduced in patients with CFA. Whether they are reduced in those cases of developing lung cancer is unknown, although study of T-cell subpopulations is needed before such a defect can be excluded. Macrophage-lymphocyte interaction may be also important in surveillance mechanisms. Differences in the phenotype of T cells and macrophages have been detected in the BAL fluid of patients with dermatomyositis/polymyositis and systemic sclerosis. Alveolar macrophages in patients with CFA are activated and appear to contain less lysosomal enzymes than in control subjects. It is conceivable that such continuous stimulation of macrophages, perhaps by immune complexes, alters their capacity to maintain a normal surveillance function.

Cytokines (ie, tumor necrosis factor-α), as well as chemotactic agents and growth factors, which are related with fibroblast chemotaxis/proliferation, such as fibronectin, platelet-derived growth factor, alveolar macrophage-derived growth factor, and insulin-like growth factor-1, promote the inflammation, destruction, and subsequent fibrosis of lung parenchyma with its permanent disorganization. Therefore, it is quite possible that changes in the lung tissue, with the subsequent epithelial atypia that follows, may predispose to the development of cancer. Furthermore, genetic alterations may contribute to lung cancer development, since p53 and p21 genes were overexpressed in hyperplastic bronchial and alveolar epithelial cells from patients with idiopathic pulmonary fibrosis (IPF). Genes p53 and p21 play an important role in the inhibition of cellular proliferation and promote the repair of tissue injury in patients with IPF. During the long clinical course of IPF, chronic DNA damage may result in mutations of the p53 gene. The loss of p53 function in tumors will lead to decreased expression of p21 and a failure to arrest in G1 in response to appropriate signals. Chronic DNA damage that might lead to p53 gene mutation may be one of the reasons of the high incidence of lung cancer in patients with IPF. Recently, genetic alterations at the level of microsatellite DNA (microsatellite instability) and loss of heterozygosity have been detected in patients with IPF with an increased rate (30%). The role of these findings in the inflammatory or malignant process is unknown, and further follow-up studies are needed.

### Pulmonary Fibrosis

A number of studies have provided evidence of an increased association between lung cancer and pulmonary fibrosis, with a prevalence ranging from 9.8 to 38% (Table 1). One of the reported series showed an excessive RR (14.2 for male smokers and 6.7 for female smokers) compared to the general population of comparable age and sex. The incidence in nonsmoking patients was much lower, supporting the idea that cigarette smoking may act as an additive risk factor for the development of lung cancer in these patients.

Contradictory to the above-mentioned studies were the findings of a large analysis of mortality data in the United States. In this study, lung cancer occurred less frequently in patients with pulmonary fibrosis (4.8%) than in patients with obstructive pulmonary disease (10.06%) and asbestosis (26.6%) compared to the general population (6.48%). In this study, although a large number of death certificates were examined (26,866,600 deaths in a 13-year period, with 107,312 deaths in patients with pulmonary fibrosis), there are limitations: it is difficult to exclude the possibility that the diagnosis of pulmonary fibrosis was not included in the death certificate, particularly if it was mild and unrecognized. Furthermore, it is difficult to determine whether long-term survivors of pulmonary fibrosis had different rates of lung cancer than short-term survivors, because of missing data on the duration of the disease. Nevertheless, the findings of such a large series challenge seriously the prevalent attitude about the correlation of IPF and lung cancer.

<table>
<thead>
<tr>
<th>Source</th>
<th>Cases of Pulmonary Fibrosis, No.</th>
<th>Cases of Coexistent Lung Cancer, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spain, 1957</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Stack et al, 1965</td>
<td>96</td>
<td>4</td>
</tr>
<tr>
<td>Meyer and Liebow, 1965</td>
<td>19</td>
<td>4</td>
</tr>
<tr>
<td>Haddad and Massaro, 1968</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Faire and Greenberg, 1973</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td>Turner-Warwick et al, 1980</td>
<td>205</td>
<td>20</td>
</tr>
<tr>
<td>Kawai et al, 1987</td>
<td>47</td>
<td>8</td>
</tr>
<tr>
<td>Nagai et al, 1992</td>
<td>99</td>
<td>30</td>
</tr>
</tbody>
</table>
In the majority of the studies, lung carcinomas were peripheral and located in the lower lobes. This finding is in accordance to the distribution of the severity of fibrotic lesions in patients with IPF, implicating the inflammatory procedure and bronchiolar squamous metaplasia in the pathogenesis of lung cancer. Squamous cell carcinoma was the most common histologic type (47%) in male patients, and adenocarcinoma was most common in female patients (64%). Lung cancer did not seem to correlate with longer or shorter survival from the onset of the disease, or with more severe initial radiographic changes. Moreover, the distribution of histologic types was not different from that found in patients with lung cancer without pulmonary fibrosis.

The incidence of synchronous multiple lung tumors has been studied less frequently in patients with IPF. In one study, the clinical features showed higher rates for male, smoking patients, with predisposition for the lower lobes and a peripheral location. A striking difference with a significantly higher incidence of small cell lung cancer was observed. The most common combinations were between squamous cell carcinoma-small cell carcinoma and adenocarcinoma-small cell carcinoma. In the large review article by Rohwedder and Weatherbee, the most common combinations were squamous cell carcinoma-small cell lung cancer, squamous cell carcinoma-squamous cell carcinoma, and squamous cell carcinoma-adenocarcinoma, in 77 synchronous cases.

In a 1999 study, a quantitative assessment of the metaplastic epithelia in the honeycombed areas revealed that squamous metaplasia, but not cuboidal cell metaplasia or bronchial cell metaplasia, occurred more frequently in patients with IPF (usual interstitial pneumonia pattern [UIP] on histology) with lung carcinoma than in UIP without lung carcinoma (p = 0.02). The degree of atypical squamous metaplasia was not different between the two groups. The authors speculated that the quantitative predominance of squamous metaplasia in the honeycombed areas may not be a precursor for lung carcinoma, but might reflect a constitutional susceptibility of patients with UIP to develop lung carcinoma. Finger clubbing was much more common in patients with IPF and lung cancer (95%) than in those with IPF and without lung cancer (63%). The cause of this phenomenon is unknown and often precedes the clinical evidence of the cancer.

**Sarcoidosis**

The association of sarcoidosis with malignancy has been addressed in several studies with conflicting results. This is due to the clinical and radiographic features of the disease, which may be similar with malignancies such as lymphoma or lung cancer, sometimes lacking a histologic confirmation. Moreover, sarcoid-like granulomas may be observed in the vicinity of a tumor or in the regional lymph nodes, usually in younger patients. This may not indicate metastatic disease and does not necessarily indicate sarcoidosis, but probably represents a local reaction or resistance to cancer cells, since no other physiologic and laboratory findings were observed. Therefore, cases of the above-mentioned malignancies may be initially misdiagnosed as sarcoidosis and vice versa, making a biopsy necessary.

Evidence of a causal relationship between sarcoidosis, lymphoma, or lung cancer comes from a number of studies. Brincker and Wilbek studied 2,544 patients and found that lymphoma and lung cancer occurred 11 times and 3 times, respectively, more frequently in patients with sarcoidosis.

In a linkage analysis of 243 cases observed for 24 years, sarcoidosis and malignancy were etiologically related in about 25% of 12 cases in which both were present. In another large study from Japan, 1,411 sarcoidosis patients were followed up for a 3-year period. Excess death was investigated using standardized mortality ratio and was found for leukemia and uterine cancer to be 5.8% and 8.7%, respectively. The number of patients with lung cancer was very small (n = 3), while other forms of cancer, such as gastric, hepatic, and colonic, were not observed.

In a retrospective cohort study with 474 patients, the RR of lung cancer was doubled during the first decade of follow-up, and thereafter it was significantly decreased. In the same study, the association of sarcoidosis and malignant lymphoproliferative disease was so constant that the authors suggested the existence of a sarcoidosis-lymphoma syndrome, in which the chronic active type of sarcoidosis appears to be responsible for an increased risk of malignant transformation of lymphoid cells. Similarly, Marschke recorded an overrepresentation of lymphoma but an underrepresentation of lung cancer in 2,700 cases of sarcoidosis. Studies challenge the existence of a sarcoidosis-lymphoma syndrome.

Seersholm et al followed up 254 patients for a median of 25 years. They registered 5 cases of lung cancer among 33 types of cancers compared to the 2.5 cases and 23 types that were expected. No lymphoma was found and only one case of leukemia occurred, a finding that prompted the authors to suggest that previous correlations were probably due to misclassification. Similarly, Romer et al failed to demonstrate a high risk of malignancy in patients with sarcoidosis. It is worth mentioning that in all studies, the patients with cancer were older than...
those without cancer, which probably reflects the increased cancer rate in older people. Table 2 shows the reported studies of lung cancer in patients with sarcoidosis.

In summary, although the “true” incidence of sarcoidosis is virtually unknown due to the symptomless and often self-limiting course of the disease, accumulative evidence suggests a high risk for lung cancer and malignant lymphomas in patients with sarcoidosis. The reason for this is still obscure. However, the increased incidence of lymphoma may be a result of the immunologic defects often noted in patients with sarcoidosis, as it happens in patients with various immunologic defects.34

**Systemic Sclerosis**

A number of studies indicate an increased risk of carcinoma of the lung in patients with scleroderma (Table 3), even in nonsmokers.35 In a large cohort of 917 Swedish patients with systemic sclerosis, the standardized incidence ratio for developing cancer was 1.5 (95% confidence interval [CI], 1.2 to 1.9). Lung cancer had the strongest association with the disease with a 4.9-fold increase, and was usually adenocarcinoma or the squamous cell type. Carcinoma of the lung followed the diagnosis of systemic sclerosis by 5 to 9 years, although the study,36 due to its design, was not able to determine the prevalence of pulmonary fibrosis or tobacco consumption.

In another study, Peters-Golden et al35 followed up 71 patients with systemic sclerosis for a mean of 5 years. During this period, three cases of lung cancer were observed in the group (RR, 16.5). All three patients had either radiographic or pulmonary function evidence of pulmonary fibrosis. No association between cancer development and smoking was found.

In the study of Winkemann et al,37 14 cases of lung cancer occurred in a population of 3,550 patients with scleroderma. Scleroderma preceded the diagnosis of lung cancer by at least 6 years in eight cases.

### Table 2—Reported Studies of Lung Cancer in Patients With Sarcoidosis

<table>
<thead>
<tr>
<th>Source</th>
<th>Cases of Sarcoidosis, No.</th>
<th>Cases of Coexistent Lung Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brincker and Wilbek, 197424</td>
<td>2,544</td>
<td>9</td>
</tr>
<tr>
<td>Yamagushi et al, 199111</td>
<td>1,411</td>
<td>3</td>
</tr>
<tr>
<td>Reich et al, 199528</td>
<td>243</td>
<td>1</td>
</tr>
<tr>
<td>Seersholm et al, 199723</td>
<td>254</td>
<td>5</td>
</tr>
<tr>
<td>Romer et al, 199827</td>
<td>555</td>
<td>4</td>
</tr>
<tr>
<td>Askling et al, 199932</td>
<td>474</td>
<td>5</td>
</tr>
</tbody>
</table>

The most frequent type of carcinoma in this series was small cell carcinoma, which accounted for 5 of the 14 cases.

In another retrospective chart review38 of 248 patients, cancer developed in 18 patients (7.3%). The most common malignancies were breast (n = 5) and lung cancer (n = 7). Lung cancer in particular was always associated with the presence of pulmonary fibrosis, which preceded the development of cancer by an average of 9 years.38 Similarly, with the report of Rosenthal et al,36 the usual histologic types were adenocarcinoma and squamous cell carcinoma. Systemic sclerosis was found to be a significant independent predictor of cancer, since gender, smoking status, type of scleroderma, and penicillamine therapy were not found to differ significantly in these two groups. Furthermore, Roumm and Medsger39 also found a 5% incidence of lung cancer in a group of 262 patients with scleroderma, which occurred in the setting of long-standing pulmonary fibrosis, but was not associated with cigarette smoking. In addition to lung cancer, other malignancies, such as breast cancer,38,39 skin cancer,36,38 and cancers of the hematopoietic system,36 have been observed with an increased incidence in patients with scleroderma.

Immunologic abnormalities noted in patients with systemic sclerosis indicate the possibility of an altered immune response that, combined with the local fibrotic changes of the lung, may predispose to cancer development, or provide a common etiologic link.40 Substances secreted by malignant cells may be directly responsible for the scleroderma changes, as occasionally seen with the carcinoid syndrome.41 The possibility of scleroderma causing organ damage that predisposes to malignant changes has been suggested, as lung cancer almost invariably develops late in the course of systemic sclerosis and in the presence of preexisting pulmonary fibrosis.38

### Dermatomyositis/Polymyositis

An association between lung cancer in patients with polymyositis was first noted in 1916.42 Since
then, an increased risk of cancer in patients with dermatomyositis/polymyositis has been shown in many studies\textsuperscript{43–45} from different countries, but this relationship is not uniform\textsuperscript{46} and the long-term risks are poorly understood. Estimates of the associated risk vary widely (from 6 to 60\%), with a cancer rate five to seven times higher that of the general population.\textsuperscript{47} Cancer is one of the main causes of death in patients with dermatomyositis/polymyositis and it significantly affects prognosis.\textsuperscript{45} 

Sigurgeirsson et al\textsuperscript{45} studied the incidence and mortality rate from cancer in 788 patients. Of the 396 patients with polymyositis, cancer developed in 9% at the same time or after polymyositis was diagnosed. The RR of cancer was 1.8 in male patients and 1.7 in female patients. Eighty-four male patients and 85 female patients died; in 24 of them (14\%), cancer was the principal cause of death. Of the 392 patients with dermatomyositis, 15% had cancer develop at the same time or after dermatomyositis was diagnosed, and the RR of cancer was 2.4 in male patients and 3.4 in female patients.\textsuperscript{45} Similarly, in the study of Chow et al,\textsuperscript{44} in which 539 patients were included, the cancer risk ratio was elevated in patients with dermatomyositis (standardized incidence ratio [SIR], 3.8) and to a lesser extent polymyositis (SIR, 1.7).

The diagnosis of cancer may precede, coincide, or follow the diagnosis of dermatomyositis/polymyositis.\textsuperscript{43,44,46,47} Cancer risk declined steadily after the diagnosis of dermatomyositis/polymyositis, with no significant excess after the first 2 years.\textsuperscript{44} It has been suggested\textsuperscript{43,44} that polymyositis and dermatomyositis often occur as a paraneoplastic syndrome; therefore, a search for an occult neoplasm must be considered seriously. The histologic type of malignancies did not seem to differ from those found in the general population. Lung cancer, and cancer of the stomach, ovaries, and lymphomas are among them.\textsuperscript{48}

The pathogenic mechanisms between polymyositis/dermatomyositis and malignancy remain unclear. There may be a common genetic and environmental cause, or malignancy may be induced by the immunosuppressive therapy of the disease. Another possibility is that myositis consists a paraneoplastic syndrome mediated by circulating immune complexes induced by the underlying malignancy. Recently, cytokeratin 19 fragment levels were found to be increased in the serum of patients with dermatomyositis/polymyositis, and the cytokeratin 19 fragment has been suggested as a useful variable to evaluate the activity of lung injury.\textsuperscript{49} To our knowledge, the possible relation of the interstitial disease that may accompany polymyositis and dermatomyositis and the development of lung cancer has not yet been examined.

**Sjögren Syndrome**

Sjögren syndrome may have various pulmonary complications, such as desiccation of the upper respiratory tract, diffuse ILD, airway obstruction, parenchymal nodules, and bronchiectasis. It may be primary or secondary to collagen diseases such as rheumatoid arthritis (RA).

Primary Sjögren syndrome is associated with increased incidence of lymphoma\textsuperscript{40,51} with an RR up to 43.8.\textsuperscript{52} Lymphoma frequently involves the lung, so that it must be included in the differential diagnosis of pulmonary lesion in such patients.\textsuperscript{53} However, an increased incidence of Sjögren syndrome has been found in patients with non-Hodgkin lymphoma.\textsuperscript{54} The mean interval between the onset of the disease and the diagnosis of lymphoma was 5.4 years in one series\textsuperscript{53} and 6.3 in another series\textsuperscript{50} with a follow-up period of 12 years. Prognostic factors for lymphoma development may be the detection of κ and λ light chains,\textsuperscript{55} heavy-chain gene rearrangements in labial salivary glands,\textsuperscript{56} mixed monoclonal cryoglobulinemia,\textsuperscript{57} as well as extraglandular manifestations of the syndrome.\textsuperscript{50}

**RA**

RA is associated with increased mortality and an increased occurrence of hematologic malignancies, especially lymphomas. In a study of 489 patients with RA followed up for a mean of 12.2 years, lymphoproliferative malignancies developed in 10 patients (2.2\%). There was an increased risk for hematopoietic cancer (SIR for male patients, 2.13; 95% CI, 1.7 to 2.7; SIR for female patients, 1.76; 95% CI, 1.5 to 2.1); lung cancer (SIR for male patients, 1.32; 95% CI, 1.2 to 1.5; SIR for female patients, 1.44; 95% CI, 1.3 to 1.6); and prostate cancer (SIR, 1.26; 95% CI, 1.0 to 1.6).\textsuperscript{58} Similarly, in the study by Mellemkjaer et al,\textsuperscript{59} consistent excesses of non-Hodgkin and Hodgkin lymphomas were found in both sexes. Risks for lung cancer and nonmelanoma skin cancer were also increased, with no predilection for any specific histologic subtype, while the risk for colorectal cancer was reduced.\textsuperscript{59} Similarly, a reduced risk of colorectal malignancy was found in another RA study,\textsuperscript{60} (SIR, 0.52; 95% CI, 0.25 to 0.96). In this study,\textsuperscript{60} a significant excess of leukemia was reported (SIR, 2.47; 95% CI, 1.12 to 4.69), whereas the incidence rates for Hodgkin and non-Hodgkin lymphomas and all other site-specific malignancies were not significantly different from general population rates. The risk reduction of colorectal cancer may be related to long-term nonsteroidal anti-inflammatory drug use in patients with RA, as has been suggested
in several other studies of long-term nonsteroidal anti-inflammatory drug use.

The positive association between RA and hematologic malignancies is incompletely understood. This may be due to the persistent immune stimulation associated with RA itself. Monoclonal paraproteinemia is slightly increased in patients with RA. It indicates monoclonal B-cell proliferation and carries a high risk of malignant transformation.

IgA paraprotein seems to carry a higher risk than IgG, while other factors such as urinary free light chains and the presence of secondary Sjögren syndrome are of less prognostic significance. Lymphomas occurring in patients with rheumatic disease have the features of those occurring in immunosuppressed patients. This may suggest an impairment of the immune system secondary to the rheumatic disease; it may be due to the treatment given for the rheumatic disease, or to a combination of these factors. For example, a role for cyclophosphamide and cyclosporin A, particularly in bladder cancer, has been suggested. In one study, the risk of malignancy in patients with RA treated with oral cyclosporin A continued even 17 years after discontinuation of the drug. The risk factors for lymphoma developing in patients with RA receiving methotrexate include severe disease, intense immunosuppression, genetic predisposition, and an increased frequency of latent infection with pro-oncogenic viruses, such as Epstein-Barr virus. The spontaneous remission of lymphomas after methotrexate treatment was discontinued highlights the likely causative role of the drug in the development of these malignancies.

Patients treated with alkylating agents have shown an increased risk for the development of acute nonlymphocytic leukemia, and both alkylating agents and azathioprine were associated with the development of non-Hodgkin lymphoma. It seems that immunosuppression favors the development of non-Hodgkin lymphoma, which includes the excess of malignancies found in transplant recipients and patients receiving long-term renal dialysis. In summary, the observed increased risk of cancer in patients with RA could be due to shared host susceptibility to both diseases, shared risk factors, RA-caused changes predisposing to cancer, or the treatment of the disease.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic, multisystem, autoimmune disorder that primarily affects women. Although morbidity and mortality have improved, an increased risk of malignancy in patients with lupus has been shown in some but not all studies.

In a cohort of 1,585 patients with SLE, a significant excess of non-Hodgkin lymphoma was found (RR, 5.2; 95% CI, 2.2 to 10.3). In addition, a significantly increased RR was found for cancer of the lung (RR, 1.9), the liver (RR, 8.0), and the vagina/vulva (RR, 5.7). Similarly, an increased risk of malignancy was observed in women with SLE. The SIR for malignancy for all women with SLE was 2.0 (95% CI, 1.4 to 2.9), and lung cancer was the only individual cancer increased in all women (SIR, 3.1; 95% CI, 1.3 to 7.9). Breast cancer was the only individual cancer increased in white women with SLE (SIR, 2.9; 95% CI, 1.4 to 0.4).

In addition, a significantly higher incidence of cervical atypia was found in women with SLE (35.9%) compared with non-SLE control groups, regardless of previous cytotoxic therapy (p < 0.01). Three cases of cervical intraepithelial neoplasia were revealed among the cases with atypia; therefore, women with SLE are encouraged to have regular cytologic cervical smears.

In a cohort of 276 patients with SLE from the United Kingdom who were followed up prospectively between 1978 and 1999, the overall estimated risk for all cancers was not increased (SIR, 1.16; 95% CI, 10.5 to 2.1). However, SLE was associated with an increased risk of Hodgkin’s lymphoma compared with the general population (SIR, 17.8; 95% CI, 0.45 to 99.2). Similarly, in the study of Abu-Shakra et al., the overall estimated risk for cancer was not increased in the SLE cohort (SIR, 1.08; 95% CI, 0.7 to 1.6). A 4.1-fold increased risk for hematologic cancers was observed, due mainly to an increased risk of non-Hodgkin lymphoma. The risk for cancer was significantly lower in the SLE cohort compared with patients with RA and systemic sclerosis.

There seems to be a positive association between SLE and non-Hodgkin lymphoma. Other cancers with a possible virus-related etiology, such as liver and vaginal/vulva cancer, are also observed in excess. Several factors probably play a role in the etiology of malignancies associated with SLE, including intrinsic disturbances of immunity and concomitant immunosuppressive therapy. There are no predictive indicators for malignancy, and immunosuppressive therapy may be a contributing factor, although there have been no reports of malignancies associated with such treatment regimes. Long-term follow-up and a multicenter effort are needed to refine risk estimates of cancer in patients with lupus.
Histiocytosis X

Histiocytosis X is a multisystem disease that frequently involves the lung, resulting in ILD without volume reduction. Carcinoid tumors of the lung, lymphoma, and mediastinal ganglioneuroma, as well as extrapulmonary carcinomas have been reported and may precede, follow, or occur concomitantly with the diagnosis of the disease.72

The incidence of lung cancer was high in patients with histiocytosis X in two series: three cases among 21 patients in one study,72 and five cases among 93 patients in the other study.73 Smoking must be an important risk factor in these patients, as patients in whom cancer developed were smokers with greater cigarette consumption than control subjects, so that the diagnosis of histiocytosis X strongly advocates the discontinuation of tobacco smoking and long-term medical follow-up.73

The reason of the high incidence of lung cancer in patients with histiocytosis X has not been clarified. Langerhans cells that have been found in the vicinity of tumor cells in some patients with bronchioalveolar cell carcinoma, and the atypical bronchiolar and alveolar cells in patients with histiocytosis X may link the two diseases etiologically.74 However, histochemical stain for S-100 protein and study of lymphocytes and Langerhans cells from patients with histiocytosis X and from patients with adenocarcinoma of the lung detected a number of differences, making the above-mentioned relationship a matter of controversy.75

OCCUPATIONAL LUNG DISEASES

Asbestosis

Experimental evidence suggests that mineral fibers are capable of causing pulmonary fibrosis and malignancy. However, penetration, retention, and phagocytosis are affected by size, shape, reactivity, and physicochemical properties.76 Thus, it is not surprising that in man the results of exposure vary considerably with fiber type and industrial process. The fact that asbestos exposure is associated with malignancies, especially mesothelioma and lung cancer, has been long recognized by experiments in animals.77 Studies78–80 in humans suggest a close relationship between asbestosis (the development of ILD induced by asbestosis) and lung cancer. It seems to be specific for asbestosis, since, for example, lung cancer develops in its presence much more often than in patients with pulmonary silicosis. Asbestos exerts a carcinogenic effect even in the absence of smoking, whereas it acts synergistically when both risk factors are present.81

Different types of asbestos bodies have been found in patients with lung cancer during autopsy. The number of asbestos bodies found in the lungs of 158 subjects suggests that 70.4% of the 51 diagnosed cases of lung cancer could be attributed to asbestos exposure, while there was significant asbestos exposure in 38.4% of 107 subjects without cancer.80

Most epidemiologic studies that have considered the relationship between the dose of asbestos and the risk of lung cancer have produced results consistent with an approximately linear relationship between dose and mortality with no threshold dose below which there is no increased risk for lung cancer.82 Age at the time of exposure does not seem to affect the RR produced by asbestos exposure.83

The latent period is variable. Some cases occur 5 to 9 years after the onset of exposure, but the risk rises until at least 30 years after first exposure.83 A study84 of amosite factory workers suggested that the latent period might be shorter when first exposure occurs at older ages, while a study85 of chrysotile miners found no evidence of a relationship between latency and dose. Lung cancer in asbestos workers arises principally in the main bronchi and occurs in all the common histologic forms, including squamous cell, small cell, adenocarcinoma, and large cell carcinoma. It can also arise in the smaller bronchi and in the peripheral parts of the lung.86

Increased lung markings are present radiologically more often in asbestos workers with lung cancer in whom lung biopsy reveals fibrosis, although random biopsy specimens may miss it. In patients without parenchymal opacities, there was a 56% excess of lung cancer in patients who had a high probability of occupational asbestos exposure at least 15 years before, with some—albeit weak—evidence of a relation with duration of exposure.87 Nevertheless, it has been shown88 that asbestos is associated with lung cancer even in the absence of radiologically apparent pulmonary fibrosis.

The mechanisms by which asbestos causes lung cancer remain a matter of speculation with various plausible but unproven hypotheses.89,90 Epidemiologic evidence suggests that asbestos acts at one or more of the later stages in carcinogenesis of lung cancer, and it may be a tumor promoter.90 Asbestos may augment the carcinogenic potential of polycyclic aromatic polycarbons, which are constituents of cigarette smoke and air pollution. This may occur as a result of absorption of carcinogens onto the fibers, resulting in their persistence in lung tissue. The greater persistence of amphiboles in tissue may be a factor in their greater carcinogenicity. Interactions between asbestos fibers and target cells may lead to genetic alterations, such as activation of oncogenes, or inactivation of tumor suppressor genes. These alterations may occur as a result of direct effects of...
fibers on chromosomes, or via genetic damage induced by the oxidant action of reactive oxygen species produced when phagocytes engulf asbestos fibers. In addition, long-term exposure to asbestos leads to the enhanced release of significant amounts of interleukin (IL)-1β, tumor necrosis factor-α, IL-6, and prostaglandin, which have activity for the fibroblast, even in the absence of overt fibrosis.91

Furthermore, asbestos has shown to impair the function of natural killer (NK) cells, an important defense mechanism against cancer. In the study by Robinson,92 all types of asbestos caused a dose-related suppression of the ability of NK cells to lyse tumor cells. Moreover, a reduction in circulating CD16+ lymphocytes, a subset of NK cells, was found in patients with dermatomyositis/polymyositis and was correlated with the duration of asbestos exposure.92 Nowadays, occupational asbestos exposure is considered to be one of the important risks for the development of lung cancer; therefore, frequent and accurate observation is necessary.

Silicosis

The risk of lung cancer in patients with silicosis, another common occupational lung disease, is not clear. Although there is sufficient evidence for the carcinogenicity of crystalline silica in animals,93 its carcinogenicity in humans was until recently a matter of controversy.94 A number of cohort and case-control studies consistently suggest an excess of lung cancer in individuals with occupational silica exposure (RR, 2 to 4), although it is difficult to exclude the confounding factor of smoking.95

The International Agency for Research on Cancer defined nine cohort studies that provided the least confounded examinations of an association between crystalline silica and lung cancer: three studies of the stone and quarrying industries; five studies of the ceramics, pottery, and related industries; and one study of gold miners in the United States. The risk of lung cancer in the three cohorts from the stone and the quarrying industries varied between 1.05 and 1.19 compared with the general population, and up to 1.93 compared with the local population. In subgroups, however, higher risks were reported.96–98 The RR of lung cancer in the five studies99–103 of the ceramic industries varied from 0.58 to 1.51; smoking did not account for the high incidence of lung cancer in silicotic patients, as a large number of smoking patients were not characterized by increased risk of lung cancer. Silica may act as a direct carcinogen or indirectly by the absorption of cocarcinogens, such as polyaromatic hydrocarbons from cigarette smoke, or industrial pyrolysis products. It may also increase the effective dose and duration of exposure to these carcinogens by impairing pulmonary clearance. Pulmonary fibrosis itself may be a precursor for the development of lung cancer.94 In the absence of lung fibrosis, the evidence of an association between silica and lung cancer must be considered to be scanty and inconsistent, but still biologically plausible.104

In a recent study,105 patients with pneumoconiosis and diffuse ILD had an exceedingly high concurrence of lung cancer compared with pneumoconiosis patients without ILD (53% vs 15%, p < 0.001). Pathologic examination revealed that dysplasias were significantly more frequently observed in peripheral bronchioles of patients with pneumoconiosis and ILD.105 These findings may suggest a positive causal relationship between pneumoconiosis and peripheral-type, single-cell carcinomas of the lung, and further indicate a pivotal role of diffuse fibrosis for the high incidence of lung cancer in patients with pneumoconiosis and ILD.

Beryllium

Beryllium has been shown to be carcinogenic in animal models.106 The International Agency for Research on Cancer has reclassified beryllium as a class-1 human carcinogen.107,108 Epidemiologic studies in beryllium-exposed industrial workers showed an increased risk of lung cancer.109,110 Histologically, beryllium-induced tumors vary mostly from adenocarcinoma to bronchioalveolar cell carcinoma.106 Similar conclusions were derived from two other studies111,112 of beryllium-exposed workers, with standardized mortality ratios ranging from 1.26 to 2.0. Very high exposure with acute beryllium disease increased this ratio, while neither smoking nor geographic location accounted for the increased risk for lung cancer.112

Coal Miners Pneumoconiosis

Although coal is not considered carcinogenic in itself, coal dust may contain various potentially carcinogenic organic (ie, hydrocarbons) and inorganic (ie, cadmium, chromium) agents. An increased incidence of stomach and intestinal cancers has been reported in coal miners, although the risk of stomach cancer was lower in workers with pneumoconiosis than in those without pneumoconiosis.113 This may be due to the impaired pulmonary clearance with the subsequent inhibition of coal reaching the digestive system. Other studies113,114 were not able to show a high incidence of malignancies or an excessive risk of lung cancer.

In the study by Ebihara115 of patients with pneumoconiosis-induced lung cancer, the predominant histologic type was the squamous cell carcinoma (54.2%), followed by small cell carcinoma (22.9%).
and adenocarcinoma (14.6%). Squamous cell carcinomas were located mainly in large airways, whereas adenocarcinomas were found in the peripheral lung tissue. In cases of mild pneumoconiosis, the majority of tumors were found in the right, upper, and large airways; in moderate and severe cases, tumors were found in the left, lower, and peripheral lung areas.

Katabami et al.\cite{116} suggested that pneumoconiosis-associated diffuse fibrosis may be an important accelerator toward the development of lung cancer, especially for peripheral type squamous cell carcinomas, and therefore must be carefully followed for early detection, if any, of lung cancer. It is of note that in the same study,\cite{116} pneumoconiosis-related lung cancer was associated with a significantly increased amount of cigarette consumption, although the influence of smoking remains controversial.\cite{104} Thus, further investigation is needed to determine whether smoking exerts a synergistic or additive effect on the development of lung cancer, and/or diffuse fibrosis associated with pneumoconiosis.

**SCAR CARCINOMAS**

The relation between scarring and the development of lung cancer has been a topic of interest for some time. A causal relation has been suggested by the finding of unsuspected early malignancy adjacent to scar during routine necropsies.\cite{117} For many years, the prevailing concept was that the scar formed first and that the cancer developed second as a result of epithelial atypia produced by the same injury, which allegedly caused the scar, or by high concentration of carcinogens within the scar.\cite{118} This traditional concept has been challenged by proposals\cite{119} that the scar consists of a desmoplastmic reaction to the tumor similar to that seen in other types of carcinoma, such as breast cancer. Indeed, immunofluorescent studies of the V collagen subtypes performed by Madri and Carter\cite{120} have shown that the collagen pattern in pulmonary scar cancers is consistent with ongoing fibroblastic activity, which supports the concept that the scar is a desmoplastmic response to the tumor.

Other possible mechanisms include uncontrolled epithelial hyperplasia in relation to bland fibrosis. Carcinogenic properties of some fibrogenic agents, such as asbestos, or of scar components, namely elastic\cite{121} and cholesterol,\cite{122} are also incriminated. Scarring is seen in up to 40% of surgical resections and 10% of necropsies.\cite{123} Forty-five percent of all peripheral cancers originated in a scar. More than 75% of these scar cancers were found in the upper lobes, and >50% were related to infarcts. Less than 25% were related to tuberculosis scars, while no relationship was found between smoking habits and scar cancer. The great majority (72%) of lung cancers were adenocarcinomas; 18% were of squamous cell type, while the rest were large cell undifferentiated carcinomas. The maturity of the scar was found to be a prognostic factor that was interpreted by the authors to correlate with the duration of the tumor.\cite{126} Prognosis of patients with those tumors remains controversial.\cite{127,128}

**Summary**

Various causes of ILDs are correlated with a higher incidence of lung malignancy. The fact that lung cancer is found frequently in the lower lobes or in the vicinity of preexisting scars, where fibrosis is predominant, supports a causal relationship between fibrosis (chronic inflammation) and lung cancer. However, the exact role of fibrosis as a predisposing factor for the development of malignancy is unclear at the present time. Further investigation in this respect may be helpful to clarify the molecular mechanisms of the fibrinogenesis-attributable onset of malignancy in patients with ILDs.\cite{129}

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