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Small Cell Lung Cancer

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Etiology of Small Cell Lung Carcinoma

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With regard to morphology, biology, and therapy it seems justified to consider small cell lung carcinoma (SCLC) separately from the other main forms of lung carcinoma (squamous cell, adenocarcinoma, large cell). This is expressed by the rough division of lung cancers into the small cell and non-small-cell groups. Regarding etiology, however, a separation of small cell carcinoma from the other types seems not to be justifiable and extremely difficult. Kreyberg (1962) has already combined squamous cell and small cell carcinomas into "group I tumors," pointing out that these types have common causative factors, especially environmental carcinogens, including tobacco smoking, occupational hazards, and ionizing radiation. In recent years the "unitarian" theory of the origin of lung cancers, suggesting a common stem cell, has been revived and is replacing the theory of a separate histogenesis of SCLC from the neural crest. Biochemical investigations have revealed that the L-dopa decarboxylase, the key enzyme of the so-called APUD tumors (Pearse 1969), can be detected not only in SCLC but, though at lower levels, in any morphological type of lung cancer (Baylin and Gazdar 1981). Both in lung cancer cultures and in patients (at relapse) a morphological conversion from SCLC to non-SCLC histology has been observed (Gazdar et al. 1981; Fer et al. 1983). It is therefore not surprising that most lung carcinogens are associated with more or less the entire spectrum of lung cancer types in man.

In a reasonably large number of studies no clear-cut data concerning the incidence of SCLC are available. To some extent this is due to the lack of histological standardization, especially in earlier reports. Also, the combination of SCLC with squamous cell carcinoma into group I tumors has led to the loss of some information on SCLC incidence. In recent years more detailed tumor typing has been pursued, which is indispensable for a therapeutic strategy.

The present survey on the etiology of SCLC is restricted mainly to some essential causative factors of this tumor type. For further information on the etiology of bronchogenic carcinoma, and in particular of SCLC, the reader is referred to the literature (Harris 1978; Greco et al. 1981; Zeller and Schmähl to be published).

The rate (number per 100,000/year) of SCLC varies with the time period in which the data were collected and in addition shows some regional differences. Annegers et al. (1978) calculated for the population of a county in Minnesota for the decades 1935–1954 a rate of 2.1/100,000/year in men, and for the decade 1965–1974 a rate of 6.0/100,000/year. Weiss (1981) estimated a rate of 8.8/100,000 man-years for men in Philadelphia for the period between 1951 and 1965. The relative frequency of SCLC is about 20% (squamous cell carcinoma 45%, adenocarcinoma 25%, and large cell carcinoma 10%) (Eckert et al. 1979; Katlic and Carter 1979; Hermanek and Gall 1979). Regarding the relative frequency of SCLC in different age groups, varying data can be found in the literature. Kennedy (1972)

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reported on 40 cases of lung cancer in patients below the age of 40: 19 of 26 male (73%) and 7 of 11 female patients (64%) had SCLC. Putnam (1977), on the other hand, reported a predominance of adenocarcinomas (> 40%) and only 2 oat cell and 2 anaplastic carcinomas among 16 men and 8 women less than 40 years of age with lung cancer. Altogether, however, there is an indication that SCLC is commoner in younger age groups (Kreyberg 1969; Weiss 1981).

As specific etiologic factors of SCLC the essential known lung carcinogens can be enumerated: (a) smoking, (b) radiation, (c) asbestos, and (d) chemical carcinogens. The involvement of air pollution by PAH emission in the etiology of bronchogenic carcinoma, and in particular of SCLC, cannot be satisfactorily assessed at present.

Auerbach et al. (1961, 1962) demonstrated convincingly that tobacco smoke is one of the main factors in the development of human bronchogenic carcinoma. They recorded three principal types of epithelial changes as a consequence of cigarette smoking: increase in the number of cell rows (between the tunica propria and the surface row of ciliated columnar cells); loss of cilia; and presence of atypical cells. They found a high degree of correlation between the number of cigarettes smoked and the frequency of these changes. After cessation of smoking epithelial lesions are reduced (66.6% in sections from ex-smokers versus 97.8% in sections of current smokers). In the sections from ex-smokers atypical nuclei were found in 50% versus 100% for current smokers.

The causal relationship of cigarette smoking to lung cancer is further supported by studies among Seventh-Day Adventists, the majority of whom do not smoke: those dying of lung cancer in this population group almost always have a history of smoking (Lemon and Walden 1966).

Another convincing hint that cigarette smoke acts as a lung carcinogen is the observation that the age distribution of lung cancer manifestation shifted downwards as the number of cigarettes smoked per day increased and as the age at which smoking began decreased (Weiss 1973).

Auerbach et al. (1975) found that all cell types of bronchogenic carcinomas seemed to be related to smoking to about the same degree. A comparable result was found by Beamis et al. (1975) in a study of 1,145 patients; these authors concluded that all cell types are related to cigarette smoking.

Yesner et al. (1973) concluded that the number of cigarettes smoked was directly related to SCLC but not to squamous cell carcinoma or other types. In a 10-year prospective study of 6,136 men, Weiss et al. (1972) found a dose-response relationship between smoking and well-differentiated squamous cell carcinoma, small cell carcinoma, and adenocarcinoma, whereas in the poorly differentiated squamous cell carcinoma no such correlation was found. In a study in 1,682 patients between 1962 and 1975 Vincent et al. (1977) found that regardless of the histopathology over 85% of all patients with lung cancer had been smokers. They were unable to disassociate smoking as a causative factor from any lung cancer type; among nonsmokers on the other hand they found a prevalence of adenocarcinoma, a result in line with the data of other investigators (Yesner et al. 1973). Stayner and Wegman (1982) reported in a case-control study with access to the Third National Cancer Survey that cigarette smoking was significantly associated with squamous cell, small cell, and adenocarcinoma, and that the relationship with SCLC was strongest. In the aforementioned study of Kennedy (1972) in 40 lung cancer patients below the age of 40, two-thirds of whom had SCLC, only 4 of the patients were nonsmokers.

It is striking that in women with a known smoking history a distinct increase in squamous cell and small cell carcinomas can be observed (Beamis et al. 1975; Chan et al. 1979). In 1960 the ratio of male to female lung cancer death rates reached a peak, and since then it

has been declining as result of this rapid increase in lung cancer in women (Burbank 1972). Altogether the data suggesting that smoking is a major cause of small cell lung cancer are convincing.

A further essential causative factor in human lung cancer is ionizing radiation. Investigations among uranium miners showed an increase in squamous cell, small cell, and adenocarcinoma due to inhalation of radioactive substances; the incidence of small cell undifferentiated carcinoma was increased to the greatest extent (Archer et al. 1974) (Table 1). Horáček et al. (1977) observed an increase in the frequency of small cell and squamous cell carcinomas among uranium miners; they observed no increase in the frequency of adenocarcinomas. Archer et al. (1976) observed a synergistic action between smoking and radiation exposure. The lung cancer rate in heavy smokers who had heavy radiation exposure was about 10 times the rate in nonsmokers with heavy radiation exposure, but 67 times the rate in nonsmokers with low radiation exposure.

With regard to this synergistic action of ionizing radiation and tobacco smoke in the etiology of human lung cancer, the low concentrations of polonium-210 (^{210}Po) and of lead-210 (^{210}Pb) (the parent of ^{210}Po) in inhaled mainstream smoke could also be contributory factors for the development of bronchogenic carcinomas (Radford and Hunt 1964; Martell 1975). Whole-body irradiation (Ishimaru et al. 1975) and therapeutic X-ray exposure (Court-Brown and Doll 1965) are also associated with the risk of lung cancer.

Among respiratory carcinogens asbestos plays an important role (Doll 1955). The annual world production of asbestos amounts to about 4.2 million tons (1983) and the large number of persons at risk from exposure to this mineral is of particular concern. Asbestos increases the risk both of bronchogenic carcinoma and of pleural mesothelioma. With regard to the development of bronchogenic carcinoma a striking synergism between asbestos exposure and cigarette smoking has been observed; the development of mesotheliomas after asbestos exposure is apparently not influenced by cigarette smoke (Wagner et al. 1971). Selikoff et al. (1968, 1980) demonstrated that cigarette smokers who work with asbestos are about 92 times more likely to die of bronchogenic carcinoma than those who neither smoke nor are exposed to asbestos. Asbestos workers who stop smoking have a declining risk of lung cancer compared with those who continue smoking (Hammond et al. 1979). The observations that lung cancer is almost as rare in nonsmoking asbestos workers as in those not exposed to asbestos and that asbestos-associated lung cancer is almost entirely found in smokers have raised the question as to whether asbestos is merely a mediator by which the tobacco effect is enhanced (Kannerstein and Churg 1972).

With regard to the histological types of lung cancer after asbestos exposure, Kannerstein and Churg (1972) observed no differences between an asbestos-associated group of 50 patients and a control group. SCLC occurred in 6 of the 50 asbestos-associated cases and in 8 of the 50 control cases (Table 2). Whitwell et al. (1974) found no difference in the frequency of SCLC between patients with less severe asbestosis and those with moderate and severe asbestosis (Table 3). They found an increase in the frequency of adenocarcinomas only from 25% to 38%; however, this difference was not statistically significant.

In Tables 4 and 5 some further compounds with proven carcinogenicity for human lung tissue are documented. Table 5 shows the frequency of histological types of lung cancer after exposure to some chemical agents. It is apparent that inhaled occupational lung carcinogens produce their characteristic frequency pattern including all histological types, so that a separation of adenocarcinomas as group II tumors that according to Kreyberg's hypothesis (Kreyberg 1962) are not caused by inhaled carcinogens does not seem to be

Table 1. Observed and expected bronchogenic carcinomas among U.S. uranium miners, 1950 – 1970. (Archer et al. 1974)

Radiation dose WLM[a]	Squamous cell			Small cell			Adenocarcinoma			Large cell or other		
	Observed no.	Expected no.	Ratio	Observed no.	Expected no.	Ratio	Observed no.	Expected no.	Ratio	Observed no.	Expected no.	Ratio
1– 119	0	1.25	0	2	0.30	6.67	0	0.28	0	0	0.30	0
120– 359	4	1.81	2.21	7	0.43	16.28	2	0.41	4.88	1	0.43	2.33
360– 839	6	2.10	2.86	10	0.50	20.00	0	0.47	0	1	0.50	2.00
840–1799	8	1.79	4.47	13	0.43	30.23	1	0.40	2.50	0	0.42	0
1800–3319	8	1.02	7.84	22	0.24	91.67	2	0.23	8.70	0	0.24	0
≥ 3320	4	0.30	13.33	12	0.07	171.43	3	0.07	42.86	1	0.08	12.5
Total	30	8.27	3.63	66	1.97	33.50	8	1.86	4.30	3	1.97	1.52

[a] Working level month

Table 2. Cell types of bronchogenic carcinoma associated with asbestos exposure. (Kannerstein and Churg 1972)

	Squamous cell	Anaplastic small cell	Adeno-carcinoma	Anaplastic large cell	Combined	Unclassified
Asbestos-associated Subjects	11	11	11	6	8	3
Controls	12	14	9	8	7	0

Table 3. Histological type of tumor in 86 cases, graded by severity of asbestosis. (Whitwell et al. 1974)

Cell type	Normal lung and mild asbestosis		Moderate and severe asbestosis	
	No.	%	No.	%
Squamos cell	8	28.6	11	19.0
Small cell	7	25.0	16	27.6
Adenocarcinoma	7	25.0	22	37.9
Other	6	21.4	9	15.5

justified. Although the number of cases in some studies is low, for most compounds a distinct association between exposure and the development of SCLC can be noted. The percentage of SCLC varies from 0 (vinyl chloride) to 74 (chloromethylethers). For the remaining compounds the percentage of SCLC lies between 15 and 33. The predominance of SCLC after chloromethylether (CME) exposure is noted in several reports and suggests that SCLC is a specific response to inhalation of these compounds [especially bis(chloromethyl)ether] (Figueroa et al. 1973; Thiess et al. 1973; Lemen et al. 1976a; Weiss et al. 1979). Table 6 shows the distribution of 43 cases of lung cancer by cumulative exposure to CME and by histological type. After moderate and heavy exposure the proportion of SCLC was $\geq 80\%$. Another essential observation was that 5 of the 20 cases in this study with moderate and heavy exposure were nonsmokers and that the age at which lung cancer was diagnosed in these two groups was considerable lower than in the other groups (Weiss et al. 1979). While Lemen et al. (1976a) concluded from their data that cigarette smoke might interact with CME exposure in a synergistic fashion, Weiss (1980) reported a higher risk of developing lung cancer in men who were not smoking: in a prospective epidemiological study of 125 workers 11 developed lung cancer; 6 cases were observed in 13 nonsmokers and ex-smokers and 5 in 38 current smokers. This inverse relationship between lung cancer risk and cigarette smoking in CME workers is in contrast to observations made in asbestos workers and in uranium miners. One possible explanation is that the carcinogenic effect of CME may be neutralized to some extent in smokers (Weiss 1980).

It is remarkable that in experimental animals (rats) after inhalation of bis(chloromethyl)ether the predominant histological cell type of lung carcinomas observed was squamous cell carcinoma; small cell carcinomas were not observed in rats. A single undifferentiated carcinoma of the lung was seen in 1 of 100 hamsters that died at 501 days after 334 exposures (Kuschner et al. 1975), thus confirming that the observation of small cell carcinomas is a rarity in experimental animals (Nettesheim et al. 1970; Karbe and Park 1974). After chronic intratracheal instillation of benzo(a)pyrene in 347 Syrian golden hamsters we observed 44 carcinomas of the respiratory tract; 5 of them (11%) were adenocarcinomas and the remaining cases were squamous cell carcinomas; no small cell carcinomas were observed (W. J. Zeller et al., in press). Blair (1974), on the other hand, reported a higher incidence of SCLC in experimental animals. He observed SCLC in 20 of 100 Sprague-Dawley rats after intratracheal instillations of benzo(a)pyrene with ferric oxide as carrier dust; 18 of these 20 rats, however, also exhibited squamous cell and adenocarcinomas in other areas of the lung.

Table 4. Occupational respiratory carcinogens.[Adapted from Wynder and Hecht (1976) and Frank (1978)]

Carcinogen	Latent period (years)		Approximate relative risk	Occupational groups
	Average	Range		
Arsenic	25	10 – 56	2 – 7	Smelter men, vineyard workers, sheep dip manufacturers
Asbestos		20 – 30	1.5 – 12	Insulation workers, shipyard workers
Chloromethylethers		10 – 20	7 – 24	Chloromethylether production workers
Chromium	24	3 – 58	3 – 15	Chromium ore processing pigment manufacturers
Carbon compounds including coke		15 – 20	1.8 – 3.5	Coke oven workers, gas workers, roofers, rubber workers
Mustard gas	20	10 – 27	2 – 36	Mustard gas production workers
Nickel	20	9 – 27	5 – 10	Nickel refinery workers
Radiation	25	10 – 45	1.7 – 29	Uranium miners, hard-rock miners

Table 5. Chemical agents and histological types of lung cancer. (Modified from Weiss 1981)

Chemical agent	No. of cases	Squamous cell		Small cell		Adeno-carcinoma		Large cell or other		References
		No.	%	No.	%	No.	%	No.	%	
Vinyl chloride	8	–	–	–	–	3	38	5	63	Waxweiler et al. 1976
Nickel	39	26	67	6	15	7	18	–	–	Pedersen et al. 1973; Kreyberg 1978
Cadmium	8	3	38	2	25	–	–	3	38	Lemen et al. 1976b
Arsenic	60	21	35	16	27	18	30	5	8	Axelson et al. 1978; Wicks et al. 1981
Chromate	18	13	72	5	28	–	–	–	–	Abe et al 1982
Acrylonitrile	6	4	67	2	33	–	–	–	–	O'Berg 1982
Chloromethylethers	47	2	4	35	74	5	11	5	11	Figueroa et al. 1973; Lemen et al. 1976a; Weiss et al. 1979

Table 6. Distribution of lung cancer cases in chemical workers by histological type and cumulative exposure to chloromethyl ethers. (Weiss et al. 1979)

Exposure	Cases (no)	Histologic type			
		Squamous cell		Small cell	
		No.	%	No.	%
O	15	6	40	3	20
Light	8	1	13	2	25
Moderate	10			9	90
Heavy	10			8	80

Exposure	Adenocarcinoma		Large cell		Other	
	No.	%	No.	%	No.	%
O	3	20	3	20		
Light	4	50	1	13		
Moderate	1	10				
Heavy			1	10	1	10

Table 7. Association of lung cancer types with scars, (Auerbach et al. 1979)

Histological type	Number of cases of lung cancer	Presence of scar	
		No.	Percent of total
Squamous cell	442	15	3.4
Small cell	246	0	–
Adenocarcinoma	295	59	20.0
Large cell	195	8	4.1
Mixed type	8	0	–
Total	1,186	82	6.9

Finally, in the discussion of the etiology of SCLC it must be pointed out that there is evidently no association between SCLC and lung scars. The majority of scar cancers of the lung are adenocarcinomas (Lüders and Themel 1954). Although other histological types can also be observed in patients with scars (Eck et al. 1969), it is accepted that scars play no decisive role in the etiology of SCLC. Table 7 gives the result of a review of 1,186 cases of lung cancer among 7,629 autopsied cases over a 21-year period by Auerbach et al. (1979). Of these cancers 82 were related to scars, and it is noteworthy that none of these was of the small cell type.

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Small Cell Carcinoma of the Lung: Pathological Anatomy

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Introduction

The demarcation of SCCL among malignant lung tumors is based on the light microscopic finding of relatively small tumor cells (Barnard 1926). The tumor cells of this tumor group, with sizes of 9 ± 1 μm and an average nucleus size of 7 ± 1 μm, are substantially smaller than the cells of squamous cell carcinomas, with a cell diameter of 16 ± 2.5 μm, and large cell carcinomas, with cell sizes of 40 ± 14 μm and nucleus sizes of 24 ± 6 μm (Brämer 1984; Fig. 1 and Table 1).

Data on the frequency of SCCL vary substantially. Most of the rates quoted are between 15% and 20% of all bronchial carcinomas. When referred exclusively to autopsies, SCCL accounts for up to 40% of all cases of lung cancer (Eck et al. 1969; Müller 1976). Reports based on surgical and autopsy material give about 18% SCCL (Fasske 1970; Hoppe 1974; Spencer 1977) and data from biopsy material, up to 30% of all lung cancer (Blaha 1983).

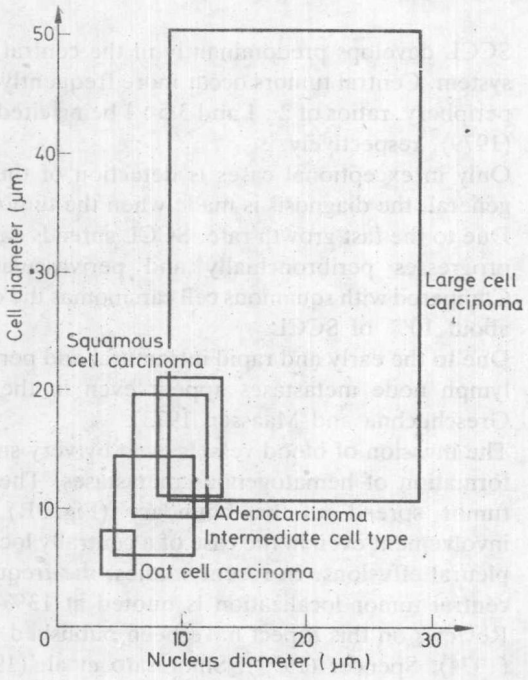

Fig. 1. Nucleus and cell diameters of different types of bronchial carcinoma; 2-sigma areas containing 95% of measured values (Brämer 1984)

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Table 1. Average diameters of nuclei and cells in different types of bronchial carcinoma, together with frequency[a] and sex ratio[b] for each

Tumor type	Nucleus Ø (μm)	Cell Ø (μm)	Nucleus proportion (%)	Frequency (%)	Sex ratio male : female
Squamous cell carcinoma	9.2 ± 1.4	13.7 ± 2.4	68 ± 8	35 – 45	7 : 1
Oat cell carcinoma	5.1 ± 0.8	6.6 ± 1.2	81 ± 10	15 – 25	4 : 1
Intermediate cell type	7.5 ± 1.3	9.8 ± 1.9	78 ± 10		
Adenocarcinoma	8.5 ± 1.3	13.2 ± 2.3	65 ± 8	13 – 23	1 : 6
Bronchoalveolar carcinoma	7.5 ± 1.0	12.1 ± 2.0	62 ± 8	1.6 – 2.4	1 : 1
Giant cell carcinoma	16.4 ± 4.3	26.5 ± 8.9	65 ± 13	14.2 – 19	
Light cell carcinoma	8.3 ± 1.3	20.8 ± 3.9	41 ± 8		

[a] Data from Müller (1980)
[b] Data from Hackl (1973) and Müller (1976)

SCCL is characterized by particularly malignant and destructive growth and tends to extensive necroses. This type of lung cancer penetrates early into lymph and blood vessels. At the time of diagnosis, metastases in liver, brain, bones, and the suprarenal glands are frequently present (Fig. 2).

Macroscopic Findings

SCCL develops predominantly in the central and intermediate sections of the bronchial system. Central tumors occur more frequently than carcinomas primarily developed at the periphery, ratios of 2 : 1 and 3.5 : 1 being cited by Haupt and Stolper (1968) and Matthews (1979), respectively.

Only in exceptional cases is detection of the defined tumor starting point possible. In general, the diagnosis is made when the tumor is already at an advanced stage (Fig. 3A). Due to the fast growth rate, SCCL spreads early and rapidly in the bronchial mucosa and progresses peribronchially and perivascularly in hilipetal and hilifugal directions. Compared with squamous cell carcinomas the circumscribed nodular tumor is found in only about 10% of SCCL.

Due to the early and rapid intramural and perivascular tumor spread, bronchomediastinal lymph node metastases appear even in the early stages of the disease (Hackl 1969; Greschuchna and Maassen 1973).

The invasion of blood vessels even by very small primary tumors explains the precocious formation of hematogenous metastases. The peribronchial and perivascular centrifugal tumor spread at the boundary (Fig. 3B) explains a relatively premature pleural involvement even in the case of a centrally located SCCL, and reflects the development of pleural effusions. In recent studies, the frequency of pleural involvement in the case of central tumor localization is quoted at 13% only (Shimosato et al. 1982).

Reviews on this aspect have been published by Giese (1960), Eck et al. (1969), Schulze (1974), Spencer (1977), Shimosato et al. (1982), and Müller (1983).