Clinical Commentary

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Environmental Associations and Histopathologic Patterns of Carcinoma of the Lung: The Challenge and Dilemma in Epidemiologic Studies

SUMMARY An update of histopathologic classification schemes is provided for carcinoma of the lung and factors that influence proportional distributions of cell types, i.e., sources and preparations of tissue specimens, observer variability, and use of secondary sources of information. Consideration is given to the natural history and to current knowledge of the demographic characteristics of cell types of carcinoma of the lung. A review of studies reporting histopathologic associations with environmental exposures suggests that no single type of carcinoma of the lung is specifically associated with exposure to tobacco smoke, arsenic, or beryllium. Furthermore, studies concerned with exposure to asbestos, chloroethers, chromates, nickel, vinyl chloride, and radioactivity lack sufficient information to conclude definitively that only one specific lung cancer cell type is associated with these exposures. In conclusion, an exclusive association of a single cell type of carcinoma of the lung with exposure to the physical or chemical agents reviewed has not been demonstrated.

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Introduction

As early as 1924, Marchesani (1) distinguished 4 types of lung cancer, and this classification was so comprehensive that it remained substantially unchanged for almost 25 yr (2). After this time, new tumor types that did not fit within this simple classification were described by pathologists, and, by 1967, the World Health Organization (WHO) recognized 13 histological types of carcinoma of the lung (2). Kreyberg (3), in 1962, proposed classification of lung cancer into 2 groups determined largely by epidemiologic characteristics of the different cell types. The Group I tumors were squamous cell and small cell carcinomas, usually located centrally in the respiratory tract. The Group II tumors were usually peripheral in location and consisted of adenocarcinomas, bronchioloalveolar carcinomas, and large cell carcinomas. At that time, there was a marked difference in smoking habits between the sexes, and Group I consisted of those cell types with a male predominance, whereas Group II had a more or less equal sex distribution. In 1971, Kreyberg (4) suggested that the Group I tumors were related to exposure to inhaled carcinogens, e.g., cigarette smoke, radon daughters, and nickel.

In addition to the recently revised WHO classification of lung tumors (5), there are 5 classifications in current use: (*1*) The Systematized Nomenclature of Medicine (SNOMED) (6), (*2*) The International Classification of Diseases (ICD-O) (7), (*3*) The Working Party for Therapy of Lung Cancer (WP-L) (8), (*4*) The Manual of Tumor Nomenclature (MOTNAC) (9), and (*5*) The Veterans Administration Lung Cancer Chemotherapy Study Group (VALCCSG) (10). The chronological development of these classification systems is outlined in figure 1. The ICD-O, SNOMED, and WHO histopathologic classifications of lung cancer have similar categories of cell types (table 1). Approximately 90% of all lung carcinomas are included in 4 main histopathologic categories: squamous cell carcinoma, small cell carcinoma, adenocarcinoma, and large cell carcinoma (16–18).

It has been suggested that lung cancer is not a single disease, and the possibility exists that there are several well-defined histopathologic types of lung cancer that tend to have unique characteristics with specific etiologies (3, 13, 16, 19–21). Numerous studies have been conducted to examine possible causal associations of environmental exposures, i.e., tobacco smoke, minerals, chemicals, and radioactive substances, with specific lung cancer cell types. Some investigators have concluded that specific chemical or physical exposures result in a greater proportion of one or more histopathologic types of carcinoma of the lung as well as an overall increased risk of lung cancer. This report discusses some of the epidemiologic characteristics of the 4 major cell types of lung cancer, factors that may affect histopathologic diagnoses, and conclusions concerning proportional distributions of the cell types. Several studies in which lung cancer cell type patterns have been associated with selected environmental exposures are reviewed.[1] It is intended that this review will be useful in the planning, conduct, and interpretation of epidemiologic studies dealing with the histopathologic types of lung cancer.

Natural History, Demographic Characteristics

A review of the biological concepts of carcinogenesis, morphogenesis, and multicentricity of lung cancer is beyond the scope of this report; however, pertinent references have been included in the bibliography (22–29).

The natural history of lung cancer is poorly defined because most studies are limited by the late stage of development at which the majority of tumors are diagnosed and by the changes in tumor histopathologic aspects resulting from radiation and chemotherapy. Lung cancers include a wide spectrum of malignant neoplasms that may be endodermal, mesodermal, or possibly neuroectodermal in derivation (30), and many are a mixture of cell types. Clinically, tumor behavior may be generalized on the basis of its cell type and degree of differentiation (31). However, it is not known whether a specific tumor will behave biologically in accord with its most differentiated or undifferentiated areas.

Several researchers have proposed different theories describing the development of lung cancer. Seydel and associates (32) proposed that during the early development of lung cancer there is a gradual transition from the normal bronchial respiratory ciliated epithelial lining to squamous metaplasia to carcinoma-in-situ and, finally, to locally invasive carcinoma, all over a period of 5 to 10 yr. Auerbach and coworkers (33) believe the pathogenesis of bronchogenic carcinoma is a continuum beginning with a few mildly atypical mucosal cells and progressing gradually to a localized area of severely atypical mucosal cells and, finally, to invasive carcinoma. They also suggest that the progressive mucosal atypia occurs over a period of many years and that carcinoma-in-situ remains as such for several years before invasion occurs. Furthermore, they indicate that at each step the process is potentially reversible. Auerbach (34) believes that this sequence of progressive mucosal atypia leading to invasive lung cancer appears to be the same, regardless of the cell type of the carcinoma.

Yesner (35) was one of the first to propose a unified concept of the histopathologic criteria of lung carcinomas and, over the past 20 yr, he has continued to refine this concept. In his studies of heterogeneous carcinomas, he describes a transition from small cell to large cell carcinomas and

[1] Terms, such as "anaplastic" and "undifferentiated," which were used in some early publications but are not used in current nomenclature have been omitted from this text.

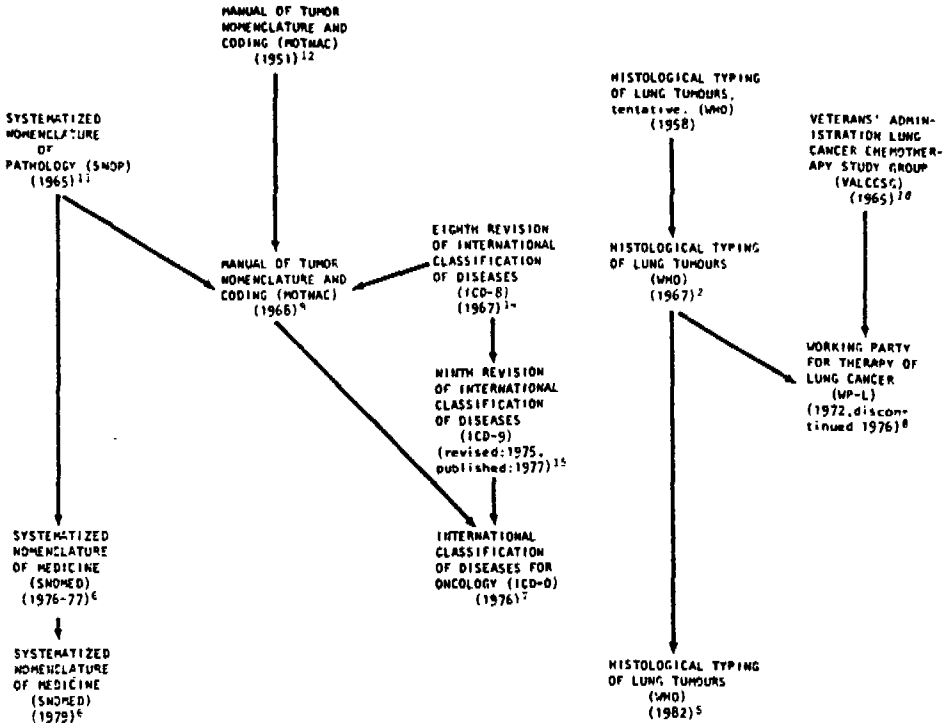

Fig. 1. Chronology and relationships among histologic classifications of carcinoma of the lung. The Manual of Tumor Nomenclature (MOTNAC) was first compiled and published in 1951 and revised in 1968 with the addition of the histologic code from Sections 8 and 9 of The Systematized Nomenclature of Pathology (SNOP, 1965) and the topographic code from Sections 140–99 in the Eighth Revision of the International Classification of Diseases (ICD-8, 1967). The SNOP was the first histologic code designed for computerization and used a 4-field organizational system, i.e., topography, morphology, etiology, and function. The SNOP was restructured and expanded into The Systematized Nomenclature of Medicine (SNOMED, 1976–77) with the addition of 2 fields: disease and procedures. The SNOMED was revised in 1979, and the morphology section dealing with neoplasms is identical to The International Classification of Diseases for Oncology (ICD-O, 1976), except that the ICD-O provides for more subtypes. The ICD-O represents an extension of Chapter 11 (Neoplasms) of The Ninth Revision of the International Classification of Diseases (ICD-9, 1975, 1977) and permits coding by topography, histology (morphology), and behavior as well as histologic grading and differentiation. Particular effort was made in developing the ICD-O to use compatible terms for neoplasms listed in The International Histologic Classification of Tumours series also published by WHO. The Histological Typing of Lung Tumours (tentative version, 1958; published, 1967) is the first of a series of "blue books" published by the World Health Organization (WHO) entitled The International Histological Classification of Tumours. The first revision of the WHO classification of lung tumors was published in 1982. The Veterans' Administration Lung Cancer Chemotherapy Study Group (VALCCSG) modified the WHO tentative (1958) histological classification in 1965. The Pathology Panel of the International Workshop for Therapy of Lung Cancer devised a classification in 1972. The Working Party for Therapy of Lung Cancer (WP-L), which was compatible both with the WHO Histological Typing of Lung Tumours (1967) and the VALCCSG classifications. The WP-L was discontinued in 1976 because chemotherapy was determined to be of little value (13) and the Lung Cancer Study Group (LCSG) replaced it in 1977. The LCSG uses a modified and condensed version of the WP-L.

from large cell carcinoma to squamous cell carcinoma and adenocarcinoma. The maturational transition from small cell carcinoma to squamous and adenocarcinoma, as described by Yesner (figure 2), is at variance with the theory that small cell carcinomas are derived from neuroectoderm. Large cell carcinoma, proposed by Yesner as a transitional stage in the maturation process, has been described as an ill-defined or "wastebasket" category (36–39). Most importantly, Yesner (40) proposed that the reporting of cell types for lung carcinomas be done with two codes, one for the predominant and the other for the secondary pattern. Other theories related to cell derivation and transition have been proposed, i.e., a single cell derivation for squamous and small cell carcinomas (41), a morphologic continuum within the general group of small cell anaplastic carcinomas (42), and a transition between the small cell carcinomas (43). These latter theories neither confirm nor refute Yesner's hypothesis, but they are indicative of the need for continued investigation.[2]

[2] Lukeman (44) believes carcinomas may arise in any portion of the lung and may or may not resemble their progenitors. He suggests that this results in the polymorphism seen in lung tumors. Carr and Lukeman (13) propose that almost all cells in the respiratory tract are capable of producing adenocarcinomas when the neoplastic process becomes initiated, and, therefore, the diagnosis of adenocarcinoma is meaningless because the term reveals nothing about the histogenesis of the cancer. They believe that the morphologic variations noted in many lung adenocarcinomas are not necessarily related to variations of a single cell or clones developing from that precursor cancer cell, but possibly from a number of cells in the respiratory tract that are capable of responding to the neoplastic stimulus. They suggest that gland formation is an expression of only one aspect of the growth pattern.

Spencer (45) observed that lung cancer may occur peripherally or centrally and that the distribution varies by cell type. He noted that peripheral tumors account for about one third of all squamous cell carcinomas, one fifth of all small cell carcinomas, and three fourths of all adenocarcinomas. Squamous cell and small cell carcinomas occur mainly in large, central bronchi, while adenocarcinomas are chiefly located peripherally and may be associated with chronic interstitial fibrosis or focal lung scars. Large cell carcinomas tend to be peripheral and subpleural in location. Carcinomas involving the conducting airways of the lung, e.g., squamous cell carcinoma, have been associated with a response to repetitive injury and chronic inflammation. The pathogenesis of small cell carcinoma is not well understood and the mechanisms of development of adenocarcinomas and large cell carcinomas of the lung are equally obscure. Squamous cell carcinomas generally grow more slowly and less often give rise to distant metastases than do small cell carcinomas, which metastasize early and widely. Adenocarcinomas tend to grow slowly but have a high metastatic potential (46).

Increases in the relative frequencies of squamous cell carcinoma (47) and adenocarcinoma (19, 48, 49) have been reported. It is not clear if the reported increases are due to changes in histopathologic criteria, increased incidence of lung cancer in women, changes in modes of therapy, and/or to environmental exposures.

Demographic Aspects (Age, Sex, and Race)

Age influences the incidence rate of lung cancer, and the rate may be proportional to the fifth or sixth power of age (50, 51). In one case series, 87% of lung cancers in men occurred in those 50 yr of age and older, and 75% of the men were 50 to 69 yr of age (52). Proportional distributions of lung cancer cell types also reflect the effect of age. The proportions of both squamous cell carcinoma and adenocarcinoma increased with age in a study of 901 cases of lung cancer diagnosed by autopsy in Los Angeles (48). Approximately 30% of the lung cancer cases, however, were described as large cell, poorly differentiated, or undifferentiated and, because of the lack of specificity of these terms, age trends of lung cancer cell types cannot be clearly determined. In a combined autopsy and surgical series of lung cancer cases identified between 1952 and 1962, 70% of the 1,324 white, male veterans studied within each of the 4 major categories of cell types were 60 to 79 yr of age (53). Diagnosis of a primary site was

TABLE 1

CATEGORIES WITHIN MAJOR CLASSIFICATIONS OF LUNG CANCER: INTERNATIONAL CLASSIFICATION OF DISEASES FOR ONCOLOGY (ICD-O), SYSTEMATIZED NOMENCLATURE OF MEDICINE (SNOMED), AND WORLD HEALTH ORGANIZATION (WHO)

O 1976 (7) and SNOMED 1979 (6)	WHO 1982 (5)
8070/3* Squamous carcinoma, NOS†	1. Squamous cell carcinoma
	Variant:
8074/3 Spindle cell type	a. Spindle cell carcinoma
8041/3 Small cell carcinoma, NOS	2. Small cell carcinoma
8042/3 Oat cell carcinoma	a. Oat cell carcinoma
8043/3 Small cell, fusiform type	b. Intermediate cell type
	c. Combined oat cell carcinoma‡
8140/3 Adenocarcinoma, NOS	3. Adenocarcinoma
8550/3 Acinar cell carcinoma	a. Acinar adenocarcinoma
8260/3 Papillary adenocarcinoma, NOS	b. Papillary adenocarcinoma
8250/3 Bronchioloalveolar adenocarcinoma	c. Bronchioloalveolar carcinoma
8230/3 Solid carcinoma, NOS	d. Solid carcinoma with mucus formation
8012/3 Large cell carcinoma, NOS	4. Large cell carcinoma
	Variants:
8031/3 Giant cell carcinoma	a. Giant cell carcinoma
8310/3 Clear cell carcinoma	b. Clear cell carcinoma
8560/3 Adenosquamous carcinoma	5. Adenosquamous carcinoma

* The 4-digit code number signifies the histologic type and the fifth digit after the slash indicates the behavior code (/3 = Malignant, primary site).
† Not otherwise specified.
‡ Multiple coding necessary, e.g., 8042/3 Oat cell carcinoma plus 8070/3. Squamous cell carcinoma.

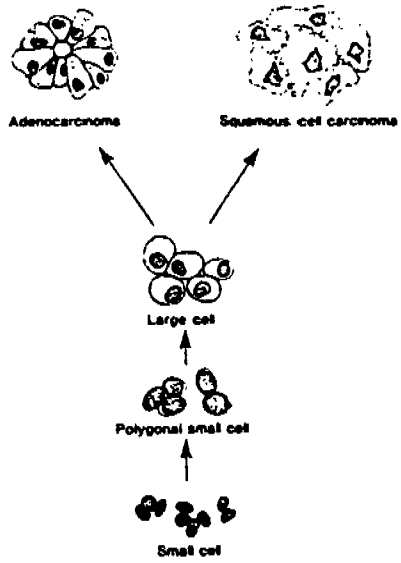

Fig. 2. Carcinoma of the lung: maturational transition of cells. Modified from Yesner (40).

uivocal in 21% of the cases in this study, d the relative frequency of lung cancer ll types might have been affected by the esence hese equivocal cases.

Kreyb (52), in an autopsy series of ıg cancer in Norway during the years 50 to 1964, reported a close similarity of : mean ages at diagnosis for squamous l carcinoma (males, 58.8 yr, versus fe- ıles, 55.6 yr), small cell carcinoma ales, 56.1 yr, versus females, 58.6 yr), d adenocarcinoma (males, 58.3 yr, versus nales, 59.8 yr). However, the proportions thin the age groups differed markedly ble 2). The proportion of squamous cell rcinoma increased consistently with age ɔm 11.5% in men 30 to 39 yr of age to .4% in men 60 to 69 yr of age. The proportion of small cell carcinoma was highest (23.2%) in men 40 to 49 yr of age and then showed a consistent decrease to only 8.3% in men 70 yr of age and older. The largest proportion of adenocarcinomas was found in men less than 40 yr of age; a slight increase occurred in those 70 yr of age and older. Women had relative frequencies of lung cancer cell types similar to those in men. Auerbach and associates (54) reported no age trend for either small or large cell carcinomas in an autopsy series of 662 men, but the proportion of squamous carcinoma tended to increase with age and the proportion of adenocarcinoma tended to decrease.

Three of these studies of lung cancer cell types by age groups are from autopsy series and are thus limited by factors determining the availability and selection of cases for autopsy (48, 52, 54). It is predicted that the peak incidence of squamous cell and small cell carcinomas may diminish in Great Britain with the death of the generation now older than 60 yr of age (45).

Inclusion of female lung cancer cases in series predominantly made up of male cases distorts the relative frequencies of cell types. The comparison of cell types of lung carcinoma in men and women discloses a preponderance of squamous cell carcinoma in men and of adenocarcinoma in women (table 3). Methods varied greatly among the studies reviewed by Modan (20) in table 3, and the wide ranges in percentages of cell types reported in men and women are evident. The Mayo Clinic series of lung cancer cell types in men and women, whether smokers or nonsmokers, agrees in part with Modan's findings (55). However, relevant background information, such as method of ascertainment, sources of tissue specimens, histologic classification, and reliability and validity, were not reported in the

TABLE 2

NUMBER AND RELATIVE FREQUENCIES (%) OF LUNG CANCER CELL TYPES IN AN AUTOPSY STUDY OF MALES IN NORWAY, 1950 TO 1974, BY AGE*

	Age Groups in Years													
	Total		< 29		30–39		40–49		50–59		60–69		≥ 70	
ll Type	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)
uamous cell carcinoma	473	62.0	0		3	11.5	53	53.5	201	64.2	177	69.4	39	65.0
ıall cell carcinoma	123	16.1	0		4	15.4	23	23.2	53	16.9	38	14.9	5	8.3
adenocarcinomas	122	16.0	5	50.0	8	30.8	14	14.1	46	14.7	35	13.7	14	23.3
Adenocarcinoma	103	13.5			4	15.4	13	13.1	40	12.8	32	12.5	14	23.3
Bronchioloalveolar carcinoma	10	1.3	2	20.0	1	3.8	1	1.0	4	1.3	2	0.8		
Bronch and tumor	9	1.2	3	30.0	3	11.5	0		2	0.6	1	0.4	0	
rcinoid	45	5.9	5	50.0	11	42.3	9	9.1	13	4.2	5	2.0	2	3.3
cell types	763	100.0	10	100.0	26	100.0	99	100.0	313	100.0	255	100.0	60	100.0

* Adapted from Kreyberg (52).

TABLE 3

RANGES AND MEDIAN VALUES FOR PROPORTIONS (%) OF CELL TYPES IN MEN AND WOMEN IN SELECTED STUDIES OF LUNG CANCER, 1952 TO 1976*

Histologic Cell Type	Male†		Female‡	
	Range	Median	Range	Median
Squamous cell carcinoma	17.9–68.9	41.3	2.9–43.1	18.6
Small cell carcinoma	0–63.6	19.4	0–44.6	11.0
Adenocarcinoma	3.2–34.1	17.9	10.2–66.7	45.1
Large cell carcinoma	0–25.0	0.3	0–19.0	0

* Adapted from Modan (20). The percentages in many studies do not add up to 100 because not all categories are included or appear in the original text.

† Studies of males from 10 countries (24 studies): U.S.A., 11; Norway, 3; U.K., 3; Austria, 1; Finland, 1; Iceland, 1; Israel, 1; Italy, 1; Singapore, 1; Uganda, 1.

‡ Studies of females from 8 countries (19 studies): U.S.A., 9; U.K., 3; Norway, 2; Austria, 1; Finland, 1; Iceland, 1; Israel, 1; Singapore, 1. Studies in which the number of men and women totaled less than 100 were not included in the ranges for women.

Mayo Clinic study; hence, interpretation of their report is restricted.

Belcher (56) has suggested that the relative frequencies of lung cancer cell types in Europeans are different from those in non-Europeans. Furthermore, the proportion of adenocarcinoma reportedly is higher in Taiwan, Tokyo, Hong Kong, Jamaica, and Kampala than that observed in European countries. Belcher also suggests that the site of origin of lung cancer differs geographically, with peripheral carcinomas accounting for over half the cases in the Far East and only 25% of the cases in Europe. These differences, however, may reflect differences in autopsy rates as well as environmental exposures.

Hinds and coworkers (57), in a review of tissue slides of 291 cases of lung cancer in women in Hawaii from 1968 to 1978, reported no difference in the distribution of cell types between Japanese and Chinese women. Lung cancers in Hawaiian women, however, were more commonly squamous cell or small cell types, whereas two thirds of the Japanese and Chinese women had adenocarcinoma. The tissue slides in this study were reviewed by 2 of the authors using the WHO classification, but the sources of specimens were not stated.

Factors That Affect Lung Cancer Cell Type Distributions

Accurate and consistent classification of lung cancer is important for both clinical and epidemiologic studies. However, such classification is complicated by numerous factors, including the changing nomenclature. As classification systems have evolved, different nomenclature has been used, thus limiting comparisons among studies. Vincent and coworkers (19) found that applying the WP-L criteria to cases diagnosed during the period from 1962 to 1968 resulted in increases in small cell carcinoma (17.0 to 22.1%), adenocarcinoma (8.7 to 17.0%), and large cell carcinoma (5.2 to 17.0%) and decreases in squamous carcinoma (51.6 to 41.2%) and undifferentiated carcinomas (12.8 to 1.4%). Sobin (58) predicts that strict application of the revised WHO criteria (5) will recategorize undifferentiated squamous carcinomas as large cell carcinomas. Also, Sobin believes that more large cell solid tumors containing mucus formation will be classified as adenocarcinoma. The large cell carcinoma category will have the poorly differentiated adenocarcinomas showing mucus formation, but it will gain the very poorly or undifferentiated squamous carcinomas.

Techniques in Obtaining and Preparing Tissue Specimens

The techniques of obtaining and preparing tissue specimens affect their quality and, subsequently, the accuracy of the histopathologic diagnosis. Because lung cancers may contain more than one cell type, each of varying differentiation, inadequate tissue sampling may result in misleading findings. For example, in the autopsy series reported by Willis (59), 23% of the lung cancers were mixed or combined cell types, whereas 77% were single cell types. Although he examined an average of 6 tissue sections of each carcinoma, he believed that some of the homogeneous tumors might have shown heterogenicity if additional tissue sections had been taken. Necrotic, inflammatory, or ulcerative areas in surgical and autopsy tissue specimens may also obscure findings.

Bronchial biopsies may be misclassified, frequently as undifferentiated small (oat) cell carcinoma, because of a "crush artifact" that has been observed in 20 to 25% or more of bronchial biopsies (13). The length of time from tissue biopsy until fixation may also affect specimen quality. Kreyberg (3) noted a greater number of combined cell types in autopsy series and attributed this to autolytic changes. Use of histochemical staining will also influence identification of various cell types. Herman and Crittenden (48) reported that with special stains for mucin the proportion of adenocarcinoma in an autopsy series increased from 10.6 to 29.0%; hence, the quality of prepared tissue specimens reflected techniques in use at the time the specimens were prepared. Histopathologic studies of lung cancer performed prior to the 1960s are limited because they lack present-day techniques of obtaining, preparing, examining, and classifying specimens.

Sources of Specimens

Numerous investigators have suggested that the source of tissue specimens for histopathologic diagnosis may influence the frequency of diagnosis of the cell types of lung cancers (10, 30, 53, 54, 60–69).

Sources of tissue specimens are determined by various diagnostic and therapeutic practices as well as the availability of autopsy specimens. The clinical mode of presentation and diagnostic techniques used may affect the detection of types of lung cancer. Centrally located tumors, such as squamous and small cell carcinomas, are more likely to provoke symptoms than peripheral tumors. The avidity with which bronchoscopy is done for persons with "central" symptoms will affect the detection of squamous and small cell carcinomas. Extensive or routine use of chest roentgenograms for early detection of respiratory diseases may lead to increased diagnosis of peripherally located tumors, such as adenocarcinoma. Thus, the style of medical care or policies of health departments or large companies could influence the detection and reporting of lung cancer cell types in different geographic regions or industries.

The treatment of lung cancer includes surgical excision, chemotherapy, or both. Because squamous cell carcinoma is thought to respond best to surgical excision (70), it constitutes a large proportion of the cell types in surgical series of lung cancer. Small cell carcinoma, the most lethal cell type, exhibits the most rapid doubling time of the major cell types and is usually treated with chemotherapy (71, 72). Consequently, small cell carcinoma is more often found in series of lung cancers derived from biopsies, cytologies, and autopsies. In Stage I adenocarcinoma of the lung, surgery is the treatment of choice, whereas radiotherapy is the preferred choice for Stage III lesions (71). Adenocarcinomas, therefore, are seen more frequently in both surgical and autopsy series than in biopsy series. The anatomic location, and particularly the stage of the lung cancer, also influences the choice of therapy. At least 50% of lung cancers have been found to be inoperable at the time of diagnosis (55, 73). Therefore, a series of surgically resected carcinomas represents at most only 50% of the cases. In addition, patients with inoperable lung cancers may not have an autopsy because the diagnosis is already known. Additional factors that may determine whether an autopsy is performed are: type of hospital, rarity of the disease, and primary mode of therapy. These various factors limit the value of an autopsy series in a review of lung cancer cell types. Herrold (53) concluded that neither surgical nor autopsy series alone are representative of the distribution of lung cancer cell types in that each has its own selection bias.

TABLE 4
RELATIVE FREQUENCIES (%) OF MAJOR LUNG CANCER CELL TYPES IN SELECTED STUDIES, 1961 TO 1977, BY TYPE AND SOURCE OF SPECIMEN*

	Source of specimens, Author(s), Date														
	Biopsy and Cytology Specimens					Surgical Specimens							Autopsy Specimens		
Investigators, date published	Yesner and associates (10) 1965	Whitwell and associates (68) 1974†	Mountain and associates (64) 1974	Feinstein and associates (31) 1974	Matthews & Gordon (30) 1977	Whitwell and associates (68) 1974†	Hinson and associates (63) 1975	Matthews & Gordon (30) 1977	Healy (60) 1980			Whitwell and associates (68) 1974†	Auerbach and associates (54) 1975	Matthews (38) 1976	Healy (60) 1980
									Total	Men	Women				
Time period	1957†	1959	Not specified	1953–59	Not specified	1950–59	1965–68	Not specified		1959–77		1950–59	1955–72	1966–75	1963–77
Cases, n	1,120	923	2,155‡	449	383	815	740	244	179	152	27	103	662	418	81
Classification	VALCCSG	WHO	TNM§	WHO	WP-L	WHO	WP-L	WP-L		WHO		WHO	WHO	WP-L	WHO
Gender, %	100	100	88	88	Not	100	Not	100	100	85	15	100	100	89	Not
	Male	Male	Male	Male	specified	Male	specified	Male	Male	Male	Male	Male	Male	Male	specified
Cell Type, %															
Squamous cell	49	41	46	36	38	57	71	56	71	76	44	17	35	30	32
Small cell	19	34	17	22	29	13	12	3	9	8	11	37	25	24	27
carcinoma															
Adenocarcinoma	18	2	24	29	23	9	9	28	12	8	33	27	25	28	27
Large cell carcinoma	16	0	9	13	9	0	7	10	8	7	11	0	14	19	14
Other‖	0	23	3	0	0	20	2	3	0	0	0	18	1	0	0

Definition of abbreviations: VALCCSG = Veterans Administration Lung Cancer Chemotherapy Study Group; WHO = World Health Organization; WP-L = Working Party for Therapy of Lung Cancer.

* Adapted from Whitwell and associates (68) and Matthews and Gordon (30).

† Whitwell and associates (68) report that a simplified version of WHO classification was used in 1961 (74).

‡ 86% of specimens were obtained from biopsy and cytology, 14% were from autopsy.

§ The TNM classification (T = tumor; N = node involvement; M = metastatic spread) is a staging system based on anatomic extent or biologic severity of the disease.

‖ Other cell types included: simplex and other; undifferentiated not specified; combined; carcinoid; sarcoma; unclassified; adenosquamous and other; mixed.

Our review of lung cancer cell type distributions reported in various studies indicates that the relative frequencies of cell types in these studies are affected by the source of tissue specimens (tables 4 and 5). Biopsy and cytology series (table 5) have higher proportions of squamous cell carcinoma (range, 36 to 49%) and small cell carcinoma (range, 17 to 34%), reflecting their central, more accessible location. Surgical series (table 5) are predominantly squamous cell carcinoma (range, 44 to 74%), indicating that surgical excision is the preferred treatment for this cell type. Autopsy series (table 5) have a predominance of small cell carcinoma (range, 24 to 37%) with wider or lower ranges in the proportion of squamous cell carcinoma (range, 17 to 35%) and adenocarcinoma (range, 25 to 27%).

Observer Variability

Histopathologic diagnoses may vary among pathologists, even though they use a similar, clearly defined, classification system. A study by Feinstein and associates (75), among 5 pathologists who reviewed 50 lung cancers, revealed a between-observer variability of 2 to 42% (most marked for poorly differentiated specimens), and a within-observer variability of 2 to 20%. Weiss and associates (76) reported only 40% unanimity among 3 pathologists in a review of 161 cases of lung cancer. The poorest agreement, 25%, occurred with small cell carcinoma. A 10-yr reevaluation of data collected during 1953 to 1959 by Yesner and coworkers (77) of 449 lung cancers indicated 63% agreement between the original and review diagnoses. A recent review of tissue biopsies of lung cancers of 476 patients was conducted by 3 pathologists, 2 of whom agreed upon the major cell type for 94% of the cases, but all 3 agreed on only 67% of the cases (78). The rates of agreement were 89% for small cell carcinoma, 86% for squamous cell carcinoma, 76% for adenocarcinoma, and 40% for large cell carcinoma.

TABLE 5
RANGE OF OBSERVED FREQUENCIES (%) FOR LUNG CANCER CELL TYPES BY SOURCE OF SPECIMEN*

Source of Specimens	Cell Type	Range in Frequency (%)
Biopsy and cytology	Squamous cell	36–49
	Small cell	17–34
	Adenocarcinoma	2–29
Surgical	Squamous cell	44–76
	Small cell	3–13
	Adenocarcinoma	8–33
Autopsy	Squamous cell	17–35
	Small cell	24–37
	Adenocarcinoma	25–27

* See table 4.

Sources of Information

There are various sources from which histopathologic information may be obtained, e.g., death certificates, physicians' reports, medical records, and pathology reports. Information in each of these sources is collected for one or more specific purposes, most likely unrelated to epidemiologic studies. It is important, therefore, that information obtained from any of these sources and intended for use in an epidemiologic study be carefully interpreted. Each source is of limited, but differing, value. The Third National Cancer Survey, 1969 to 1971, obtained information concerning 20,167 microscopically confirmed cases of lung cancer (all races, both sexes) from medical records (98% of the cases) and death certificates and cancer registries (2% of the cases) (79). Cell types were coded using the MOTNAC system and the relative frequencies were: 35% for squamous cell carcinoma (8,073), 13.6% for small cell carcinoma (8,043), 15.0% for adenocarcinoma (8,143), 27.7% for carcinoma not otherwise specified (8,013), and 8.7% for others. The reliability of secondary information on lung cancer cell types was examined in an early study by Haenszel and associates (80) who, using a sample of 247 male lung cancer deaths, compared physicians' reports with information obtained from original sources. In this comparison, adenocarcinoma was overdiagnosed by 60% and the squamous cell-undifferentiated group was underdiagnosed by about 20%. As a result of this analysis, Haenszel and associates concluded that access to the initial tissue diagnoses is essential for determination of the cell type of lung cancer.

Environmental Exposures Associated with Specific Cell Types

Specific lung cancer cell type may be an important variable in identifying and interpreting associations between specific environmental exposures and the development of disease. Unfortunately, the histopathology and pathogenesis of occupationally associated lung cancers are poorly documented, and the intensity and duration of exposure are not easily determined long after the exposure has occurred. Furthermore, mixed exposures in the workplace, cigarette smoking, age, use of inappropriate comparison groups, use of histopathologic specimens obtained from different sources, differences in early classification schemes, small numbers of cases, and mixing data of different races and sexes, compromise the interpretations of many study results.

It is possible that differences in particle size and the intensity of an exposure may have an effect on the relative frequency of lung cancer cell types in addition to the overall risk of lung cancer. Yesner (81) has suggested that the greater the insult to differences in the proximal bronchi, the more malignant is the tumor that results. He cites the occurrence of small cell carcinoma, one of the most malignant of tumors, in a study of uranium miners that demonstrated a dose-response effect for this lung cancer cell type. The almost exclusive pattern of small cell carcinoma in lung cancer cases among moderate and heavy exposures to bis(chloromethyl) ether (BCME) also suggests a dose-response effect. Abe and associates (82) observed that heavier exposure to chromate dust was associated with a higher incidence of small cell carcinoma. They suggested that when exposure to a respiratory carcinogen is less intense and of long duration, squamous cell carcinoma might become the predominant cell type of lung cancer in occupational exposures. The potency of an agent may also be a factor.

Lung cancer cell types have been reported in studies of acrylonitrile, cadmium, and mustard gas exposures. However, to date, acrylonitrile and cadmium have not been established as respiratory carcinogens. The evidence of increased risk of respiratory tract tumors after exposure to mustard gas is compromised in some studies by a question of preferential reporting of cases (83). The lung cancer cell types identified in studies of these 3 substances are not discussed in this report.

Smoking

Studies conducted during the past decade suggest that association between a single cell type of lung cancer and smoking remains equivocal (84). A survey of cell types of 1,041 primary lung cancers in U.S. veterans disclosed a significant association between cigarette smoking and Kreyberg's Group I (squamous cell carcinoma and small cell carcinoma—both predominantly centrally located); however, no correlation was found between the cell type and the amount of tobacco smoked (53). Smoking histories were obtained by mailed questionnaires.

Over a 10-yr period, Weiss and coworkers (85) followed 6,136 men and found that well-differentiated squamous cell carcinoma, small cell carcinoma, and adenocarcinoma all displayed a dose-response relation to smoking. By contrast, poorly differentiated squamous cell carcinoma (34% of the total lung cancers in the study) failed to demonstrate a dose-response pattern. Yesner and associates (77) concluded that the proportion of squamous cell carcinoma seemed unrelated to the amount of reported cigarette smoking, although the proportions of small cell carcinoma reflected a positive relationship.

Auerbach and associates (54), in a study of 662 U.S. male veterans with lung cancer, found that smoking habits, calendar year of diagnosis, and age at death all appeared to be related to the cell type of lung cancer; however, the differences were generally small, and no consistent patterns were evident. Vincent and coworkers (19), in a study of lung cancer in 584 men and 56 women at the Roswell Park Memorial Institute, reported that cell type did not appear influenced by the amount of smoking attributed to the patient, except that nonsmoking patients had a significantly higher proportion of peripheral tumors (adenocarcinomas and bronchioloalveolar carcinomas) than their smoking counterparts.

In 4 of these 5 large studies concerning smoking and cell types of lung cancers, the sources of the specimens were either not reported or were mixed (19, 53, 77, 85). Autopsy specimens were used in one study (54). Some proportion of the specimens in each of the studies was obtained in the 1950s or 1960s. Validity or reliability results on histopathologic diagnoses were reported in all 5 studies.

Minerals

Asbestos. Early studies of persons with lung cancer who had been exposed to asbestos reported high proportions of adenocarcinoma (86, 87). Nevertheless, as early as 1961, Whitwell and coworkers (74) proposed that some of the association between lung cancer cell types and environmental exposures was artifactual because histopathologic diagnoses are often based on bronchial biopsy specimens and, thus, reflect a high frequency of carcinomas that occur in the larger, more accessible bronchi, i.e., squamous and small cell carcinomas (74) (table 4). In their autopsy study of lung cancer in 88 male asbestos workers, Whitwell and coworkers (68) also demonstrated a high proportion of adenocarcinoma (table 6). However, in order to evaluate the influence of asbestosis on cell type, the investigators compared the proportion of adenocarcinoma among 28 workers with mild asbestosis (25%) with that in 48 workers with moderate to severe asbestosis (38%). They found that the apparent difference was not significant (68). Another autopsy series by Warnock and Churg (88) also demonstrated a high proportion of adenocarcinoma. Again, the source of specimens, in this case, autopsy, may have influenced the relative frequency of cell types in these latter 2 studies. Three additional studies of lung cancer cell types in persons exposed to asbestos (87, 89, 90), were based on a variety of sources of tissue specimens. In 2 of these studies the sample size was small (Hourihane and McCaughey (87), n = 17; Hasan and associates (89), n = 12); therefore, these findings do not resolve the issue. A more recent comparison of lung cancer cell types, obtained from a general hospital series, indicated no difference in the proportion of cell types for asbestos-exposed shipyard workers versus nonasbestos-exposed workers (table 7) (91). It is important to note that

TABLE 6

NUMBER AND RELATIVE FREQUENCIES (%) OF LUNG CANCER CELL TYPES REPORTED FOR PERSONS EXPOSED TO ASBESTOS

	Hourihane & McCaughey (87) 1966		Kannerstein & Churg (90) 1972		Whitwell and associates (68) 1974		Warnock & Churg (88) 1975		Hasan and associates (89) 1978	
e period	Not specified		Not specified		1962–72		Not specified		1945–72	
ssification	Not specified		WHO		WHO		WHO		Not specified	
rces of pecimen	Pathologic material		66% autopsy		Autopsy		Autopsy		42% autopsy, 58% surgery, etc.	
e of xposure	Not specified		Asbestos workers		Asbestos workers		50% mixed occupations, 50% unknown		80% shipbuilding, 20% nonship-building	
oking istory	71% smokers, 23% nonsmokers 6% unknown	30% smokers 70% nonsmokers	Not specified		88% smokers, 22% unknown	Not specified	48% smokers 4% nonsmokers 48% unknown	57% smokers 43% unknown	93% smokers	

	Men		Women		Men		Men		Women		Men		Women		Gender unspecified	
l type	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)
amous cell	5	29	2	20	11	22	9	22	2	22	8	35	2	29	4	33
all cell	4	24	1	10	11	22	23	26	3	33	2	9	1	14	2	17
enocar-inoma	6	35	6	60	11	22	30	34	3	33	11	49	3	43	6	50
ge cell	0		0		6	12	0		0		1	4	0		0	
ier*	2	12	1	10	11	22	16	18	1	11	1	4	1	14	0	

Other cell types include: undifferentiated, 2; adenocanthoma, 1; combined, 8, and unclassified, 3; simplex, 13; mixed, 4; combined, 2.

s study is the only study reviewed where l type distributions for asbestos-exposed d nonexposed lung cancer cases were mpared. The data in table 7 were not blished and were provided on request . Blot, personal communication, 1980). higher proportion of adenocarcinoma is n in the "never employed" (unexposed) oup when compared with the "exposed" oup (9 versus 5%). Thus, the question re-ins whether the apparent proportions of enocarcinoma found in various studies artifactual or whether they are truly rep-entative of lung cancer cell type distribu-ns resulting from exposure to asbestos.

senic. The association of exposure to senic and various arsenic ores with an in-eased risk of lung cancer stimulated stopathologic studies of lung cancer cell types among miners and smelter workers. The proportional distribution of lung cancer cell types identified during the period 1957 to 1963 among 25 workers in South African gold mines that contain large quantities of arsenopyrite (mispickel) was squamous cell carcinoma (28%), small cell carcinoma (30%), and anaplastic carcinoma (52%) (92). The lack of specificity of the latter designation precludes drawing conclusions regarding associations of cell types.

A high incidence rate of lung cancer in Silver Bow and Deer Lodge counties in Montana led to the first U.S. study of the histopathologic cell types of lung cancer among workers in copper mines and a copper smelter (93). The investigators speculated that the excess lung cancer among the smelter workers was related to air pollutants containing arsenic, whereas the excess among the miners was associated with exposure to decomposed quartz used for sanding streets in wintertime. Tissue slides and blocks obtained from the pathology files of 2 pathologists serving these counties were examined independently by 4 pathologists using the VALCCSG classification. The predominant cell type reported was squamous cell carcinoma (table 8) in which a large proportion (71%) among the smelter workers was poorly differentiated. The control group comprised 45 cases of lung cancer in men who had not worked longer than a year in either the smelter or the mine. The relative frequency of lung cancer cell types was similar in the control group to the frequencies in the smelter workers and miners. Observer variability, if evaluated, was not reported. The International Agency for Research on Cancer criticized the study

TABLE 7

HISTOLOGIC DISTRIBUTION FOR LUNG CANCER CASES IN COASTAL GEORGIA STUDY (91) BY HISTORY OF EMPLOYMENT IN SHIPBUILDING AND SOURCE OF CELL TYPE IDENTIFICATION*

	Source of Identification							
	Death Certificates		Brunswick Hospital		Savannah Hospitals		Total	
ng Cancer ll Type	History of Employment in Shipbuilding							
	Yes	No	Yes	No	Yes	No	Yes	No
uamous cell carcinoma	6 (14)†	20 (14)	11 (38)	38 (36)	7 (30)	45 (40)	24 (25)	103 (28)
nall cell carcinoma	3 (7)	5 (3)	3 (10)	13 (12)	1 (4)	9 (8)	7 (7)	27 (7)
lenocarcinoma	1 (2)	6 (4)	1 (3)	10 (9)	3 (13)	15 (13)	5 (5)	31 (9)
ncer cinoma NOS‡	33 (77)	113 (78)	14 (48)	46 (43)	12 (52)	42 (38)	59 (62)	201 (55)
tal	43 (100)	144 (100)§	29 (100)	107 (100)	23 (100)	111 (100)	95 (100)	362 (100)

* Data in table were supplied by William Blot, personal communication, March 10, 1980.
† Numbers in parentheses are percentages.
‡ Not otherwise specified.
§ Excludes 1 mesothelioma.

TABLE 8

NUMBER AND RELATIVE FREQUENCIES (%) OF LUNG CANCER CELL TYPES IN STUDIES OF OCCUPATIONAL EXPOSURES TO MINERALS

	Arsenic										Beryllium				Chromate				Nickel	
Investigator, date published	Newman and associates (93) 1976						Wicks and associates (96) 1981				Smith and Suzuki (97) 1980				Abe and associates (82)				Kreyberg (101) 1978	
Time period	1959–72						1950–74				1942–68				1972*				1948–74	
Classification	VALCCSG						VALCCSG				WHO				Not specified				Not specified	
Source of specimens	Histology slides and tissue blocks (54%, small biopsy and cytology) (Wicks and associates, 1981)						Autopsy	29%	Autopsy	21%	Autopsy		Biopsy		Not specified				Not specified	
							Biopsy	69%	Biopsy	74%										
							Cell block	2%	Cell block	5%										
Type of exposure	Copper Mine		Copper Smelter		Controls		Copper Smelter		Controls		Mixed occupational exposures				Chromate workers				Nickel refinery	
Smoking history	70% smokers		32% smokers		60% smokers		95% smokers		93% smokers		60% smokers		80% smokers		Cell types specified (N = 18) = 100% smokers				82% smokers	
	30% unknown		68% unknown		40% unknown		5% unknown		7% unknown		40% unknown		20% unknown						18% nonsmokers	
Cell types	(n)	%	(n)	%	(n)	%	(n)	%	(n)	%	(n)	%	(n)	%	(n)	%			(n)	%
Squamous cell	33	61	14	58	27	60	13	31	20	47	2	13	3	30	13	65			28	67
Small cell	11	20	7	28	11	24	10	24	6	14	3	20	6	60	5	25			6	15
Adenocarcinoma	5	9	3	12	3	7	16	38	5	12	7	47	1	10	0				5	13
Large cell	5	9	1	4	3	7	3	7	8	19	3	20	0		0				0	
Others*	0		0		1	2	0		3	7	0		0		2	10			2	5

For definition of abbreviations, see table 4.
* Combined cell types, not defined, Group II tumors.

because the sample was not random and the proportion of the total lung cancers in the area represented by study subjects was not stated (94).

Lung cancer cell types of 18 copper smelter workers were identified from medical files in Sweden, and specific cell types were reported, e.g., squamous cell carcinoma (95). The majority of cell types, however, were qualified as poorly differentiated to undifferentiated. These qualifications, plus the secondary source of information, make these findings inconclusive.

A carefully designed case-comparison study of 42 U.S. copper smelter workers for the period 1950 to 1974 reported a significantly higher proportion of adenocarcinoma and a high proportion of small cell carcinoma (table 8) (96). The patient's age, year of diagnosis, smoking history, occupation, as well as source of specimens and their condition and preparation, histopathologic classification, and "blind" examination of tissue slides were all carefully considered. About one fourth of the lung cancers in both study cases and compeers had no tissue available for cell typing. An autopsy diagnosis was obtained for 15 smelter workers and 12 compeers, and a surgical diagnosis was obtained for 13 smelter workers and 15 compeers. Cell types of lung cancer by source of specimen were not reported.

Beryllium. Smith and Suzuki (97) found small cell carcinoma to be the predominant cell type (60%) in biopsies of 10 workers exposed to beryllium, 1942 to 1968, and adenocarcinoma to be the predominant cell type (47%) in autopsies of 15 other workers (table 8). Pathology specimens were not received for 20 (44%) persons similarly exposed, and their cell types may not be dissimilar to those reviewed. Epidemiologic evidence that occupational exposure to beryllium may lead to an increased risk of lung cancer is limited, and the risk of exposure to beryllium compounds in the general population appears to be small (94).

Chromate. Based on worldwide studies summarized by Hueper (86), the National Academy of Science concluded that lung cancers in chromate workers do not demonstrate a predominance of a specific cell type (98). More recently, Abe and associates (82) reported 13 squamous cell and 5 small cell carcinomas identified in 20 cases of lung cancer among workers in a chromate factory in Japan (table 8). The investigators suggested that the carcinogenicity of chromate compounds may reside in the hexavalent rather than the trivalent materials and noted that the greater the occupational exposure, the greater the proportion of small cell carcinoma observed. Furthermore, Abe and associates suggested that when exposure to a carcinogen is less intense but of long duration squamous cell carcinoma might become the predominant cell type among occupationally related lung cancer. All 18 of the workers with defined cell types

were smokers, but those with squamous cell carcinoma smoked more heavily than those with small cell carcinoma. The sources of specimens and histologic classification used in this study were not reported.

Nickel. Eight studies of the histopathologic aspects of respiratory cancers in nickel workers revealed 49 lung cancers of which squamous cell, anaplastic, and pleomorphic carcinomas were the most common cell types (99). Five of the studies were published prior to 1960, two in the mid-to-late 1960s, and one report was a personal communication in 1972. A sputum surveillance program of 282 male nickel workers in a Canadian nickel sinter plant, 1973 to 1974, identified by cytologic examination 11 workers with abnormal sputum (100). Five of the men, all smokers, later developed squamous cell carcinomas diagnosed from surgical lung specimens.

A histopathologic study of 44 cases of lung cancer in nickel refinery workers in Norway, 1948 to 1974, disclosed squamous cell carcinoma to be the predominant cell type in 39 cases reported (table 8) (101). The sources from which the specimens were obtained were not specified. The majority of these workers (82%) were smokers. Nickel refining, like other industrial processes, results in exposure to multiple substances, so that an association of one cell type with a single agent is very difficult to determine without environmental measurements.

Chemicals

Bis(chloromethyl) ether. In the 1970s, several reports described an increased risk of lung cancer among employees exposed to chloroethers (102–106). Small cell carcinoma was the predominant lung cancer cell type found in 4 of the 5 studies (table 9). Only one study reported sources of specimens used for diagnosis (105); the histopathologic classification was specified in 2 studies (105, 106). Lung cancer cases (8 or less) were reported in 3 studies in which the size of the exposed groups ranged from 8 to 136 (102–104). The high proportion of cases among the exposed workers reflects the excessive risk of lung cancer associated with BCME. Confirmation of a specific cell type association with exposure to BCME is difficult, however, considering the small numbers of cases and the limited information available. The BCME-exposed workers reported by Lemen and associates (104) were enrolled in a sputum cytology surveillance program. It is not clear whether the histopathologic diagnoses were based on specimens obtained in the course of the cytologic screening program or whether diagnostic material was obtained from other sources, such as surgical or autopsy specimens.

Weiss and Figueroa (105) and Weiss and coworkers (106) studied 11 cases and 28 cases of lung cancer that occurred during the periods 1962 to 1972 and 1960 to 1977, respectively, among workers exposed to BCME. (Exposure to BCME included exposure to chloromethyl methyl ether.) All workers in the first study (1962 to 1972) had been enrolled in a screening program in a chemical plant in Philadelphia, and were less than 59 yr of age when small cell carcinoma was diagnosed. The sources of specimens were: bronchial biopsy, 3; biopsy of metastatic lesions, 3; thoracic biopsy, 2; resected lung biopsy, 2; autopsy, 1. The second report included cases of lung cancer that occurred during the period 1960 to 1977 among the same group of employees exposed to BCME. Small cell carcinoma was found to predominate the lung cancer cell types identified among the 28 workers (table 9). The specific sources of tissue specimens were not reported in the later study. The 11 workers studied in the initial study were considerably younger than those included in the larger study, e.g., 64 versus 46% were 30 to 49 yr of age. Small cell carcinoma has been found to be highest in the group 40 to 49 yr of age, with a proportionate decrease in the older age groups (table 2). The possible effect of age, as well as sources of tissue specimens, on the distribution of lung cancer cell types among workers exposed to BCME needs further clarification.

Vinyl chloride. An excess of respiratory cancer among workers engaged in the production and polymerization of vinyl chloride has been reported in 4 studies (107–110). In a cohort of 4,086 men employed at some time during the period 1942 to 1973 in a synthetic chemicals plant, 45 cases of lung cancer were identified (110). Histopathologic material was available for 27 (60%) of the lung cancer cases among the chemical workers and a matched comparison group of 50 cases of lung cancer was selected from chronologically ordered pathology logs. Histopathologic material for all cases was reviewed by a panel of pathologists unaware of the employment histories of the study subjects. The proportional distributions of lung cancer cell types were compared between the 2 groups (table 9). A greater proportion of large cell carcinoma and adenocarcinoma was found in the group of chemical workers than in the comparison group. Many workers had been exposed to a variety of substances, and it was concluded that polyvinyl chloride dust was the most likely etiologic agent. Histopathologic specimens were difficult to find among the chemical workers who died of lung cancer early in the study and who were older on the date of death. The lack of spe-

TABLE 9

NUMBER AND RELATIVE FREQUENCIES (%) OF LUNG CANCER CELL TYPES IN STUDIES OF OCCUPATIONAL EXPOSURES TO CHEMICALS

	Bis (Chloromethyl) Ether								Vinyl Chloride			
Authors, Date Published	Theiss and associates (102) 1973		Sakabe (103) 1973		Lemen and associates (104) 1976		Weiss and associates (106) 1979		Waxweiler and associates (110) 1981			
Time Period	1962–71		1955–70		1955–76		1960–77		1942–73			
Classification	Not specified		Not specified		Not specified		WHO		VALCCSG			
Source of Specimens	Not specified		Not specified		Not specified		Not specified		Not specified			
Type of Exposure	Chemical workers		Chemical workers		Chemical workers		Chemical workers		Chemical workers		Comparison Subjects	
Smoking History	75% smokers 25% unknown		100% smokers		80% smokers 20% unknown		82% smokers 18% unknown		Not specified			
Cell type	(*n*)	(%)	(*n*)	(%)	(*n*)	(%)	(*n*)	(%)	(*n*)	(%)	(*n*)	(%)
Squamous cell	0		0		0		1	4	6	22	15	30
Small c	5	63	1	20	4	80	19	68	6	22	15	30
Adenoc ma	0		1	20	0		5	18	7	26	14	28
Large cell	0		0		1	20	2	7	8	30	5	10
Other*	3	37	3	60	0		1	4	0		1	2

For definitions of abbreviations, see table 4.

* Includes: not specified (102); simple, 1; Pancoast, 1; unknown, 1 (103); undifferentiated (106); not specified (110).

cificity associated with large cell carcinoma plus the substantial proportion of cases among the workers for whom histopathologic specimens were unavailable make it difficult to interpret the significance of the findings in this study. A description of the lung cancer cell type distributions by sources of specimens and by age of study subjects, including those for whom histopathologic specimens were unavailable, might further clarify potential associations.

Radioactive Substances

Radon gas/radon daughters.[3] Among the respiratory carcinogens, radioactivity in general and uranium in particular have received the most attention. A review of the early recognition of a pulmonary disease among miners in the Erz Mountains attributes Paracelsus, in 1531, as describing "mala metallorum" among miners on the German side of the mountains (Schneeberg) and Agricola, in 1556, as describing a pulmonary disease among miners on the Bohemian side (St. Joachimstahl) (112). The pulmonary disease among the miners in Schneeberg was recognized as a malignant neoplasm by Härting and Hesse in 1879, and the disease among the miners in St. Joachimstahl was identified as being similar to that of the miners in Schneeberg by Löwy in 1929 (112). The Schneeberg and St. Joachimstahl mines produced nickel, magnesium, bismuth, and radium, and by the 1920s, it was suggested that radioactivity was the carcinogenic factor. Despite prior recognition of the risk, the incidence of lung cancer among uranium miners in the United States in the 1950s was 10 times greater than that of the general population (113). Examinations of the cell types of lung cancers among uranium workers indicated a preponderance of small cell carcinoma.

A high relative frequency of small cell carcinoma in a matched, case-comparison study of 121 cases of lung cancer in U.S. uranium miners was reported by Saccomanno and associates (114). Exposures to increasing amounts of radiation were found to result in a greater proportion of small cell carcinoma and a smaller proportion of squamous cell carcinoma. The study identified 116 "definite" and 15 "possible" lung cancer cases during the period 1949 to 1969. Five of the 15 "possible" cases were selected and included in the study to make a total of 121 lung cancer cases that were analyzed.

[3] "Ores bearing uranium include its decay products which form a series of radionuclides. One of these radionuclides is the inert gas radon, which diffuses into mine atmospheres where it decays (half life of 3.8 days) into radioisotopes of polonium, bismuth and lead which collectively have a half life of about 30 minutes. These radionuclides ("daughters" of radon) attach themselves to the nearest solid which is usually an airborne dust particle . . . a large proportion of the radon daughters is deposited in the tracheobronchial tree including some which as "free ions" are unattached to particulates in air." p. XXI (111).

TABLE 10

MEAN AGE AND MEAN CIGARETTE-PACK-YEARS FOR URANIUM MINERS BY ESTIMATED WORKING LEVEL MONTHS (WLM) OF EXPOSURE AND THEIR WORKING COMPARISON SUBJECTS (NONURANIUM MINERS)*

	701–1,200 WLM (n = 27)	Comparison Subjects	1,201–2,500 WLM (n = 24)	Comparison Subjects	2,501–9,700 WLM (n = 30)	Comparison Subjects
Mean age	55.5	58.1	53.3	62.3	53.2	65.2
Mean cigarette-pack-years	36.7	44.7	34.3	45.8	30.7	57.2

* Adapted from Saccomanno and associates (114).

TABLE 11

NUMBER AND RELATIVE FREQUENCIES (%) OF LUNG CANCER CELL TYPES AMONG URANIUM MINERS AND AGE- AND CIGARETTE-MATCHED COMPARISON SUBJECTS*

	Uranium Miners, 40–200 WLM†		Comparison Subjects		Uranium Miners, 201–700 WLM		Comparison Subjects	
Cell Type	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)
Squamous cell carcinoma	6	42.9	9	64.3	9	34.6	15	57.7
Small cell carcinoma	5	35.7	3	21.4	11	42.3	4	15.4
Adenocarcinoma	2	14.3	1	7.1	4	15.4	3	11.5
Large cell carcinoma	1	7.1	1	7.1	1	3.8	4	15.4
Other					1	3.8		
Total	14	100.0	14	100.0	26	100.0	26	100.0

* Adapted from Saccomanno and associates (114).
† Working level months.

Criteria for selection of the 5 "possible" cases were not specified, and these cases were not identified in the analyses. A comparison group of lung cancer cases among nonuranium-exposed miners was chosen and an attempt was made to match on age and smoking status. Considerable difficulty was encountered in attempting to match the cases with the comparison group of nonuranium-exposed miners on the basis of age and smoking history. Two thirds of the uranium miners were in the high exposure group: 701 to 9,700 working level months (WLM).[4] Within the two highest exposure groups, 1,201 to 2,500 WLM and 2,501 to 9,700 WLM, mean ages between cases and comparison subjects differed by 9 and 12 yr, respectively, and mean cigarette-pack-years differed by 11.5 and 26.5 pack-years (table 10). Because these 2 highest exposure groups constituted 44.6% (n = 54) of the uranium miner cases, large differences in age and smoking diminish the value of this comparison. The matching technique did not accomplish complete age-matching but it did establish more valid comparisons for the low exposure categories in which the proportion of small cell carcinoma is greater among the miners in the 40 to 200 and 201 to 700 WLM categories than among the comparison subjects (table 11).

[4] A working level month = 1.3×10^5 million electron-volts of potential alpha energy from radon daughters per liter of air in the mine in which a man works 40 h/wk for 4.5 wk.

The investigators reported that "blind" readings of tissue slides of lung cancer were not possible because the miners' lungs showed fibrosis and pigmentation. Any possible bias resulting from this problem was not estimated. In a later report on U.S. uranium miners (115), many of whom were in the early study of Saccomanno and associates (114), there were marked differences in the proportion of all cell types within different age groups (table 12). The proportion of squamous cell carcinoma shows a consistent increase in successively older age groups, i.e., from 18.5% of lung cancer in miners 40 to 49 yr of age to 50.0% in miners 70 to 79 yr of age. Small cell carcinoma, however, constituted 76.6% of lung cancer in miners younger than 49 yr of age, and the proportion then declines with age, constituting only 10% in miners 70 to 79 yr of age. Small cell carcinoma constitutes more than half (57%) of all lung cancers in uranium miners 50 to 69 yr of age, but when the grouping is younger than 55 yr of age versus 55 yr of age and older, small cell carcinoma constitutes 74.5 versus 48.3% of all the cell types. The proportionate increase of squamous cell carcinoma and decrease of small cell carcinoma within successively older age groups of uranium miners is similar to Kreyberg's study (52) (see table 2), thus emphasizing the importance of having a carefully age-matched comparison group.

A summary of the histopathologic types of carcinoma of the lung in uranium

TABLE 12

NUMBER AND RELATIVE FREQUENCIES (%) OF LUNG CANCER CELL TYPES IN 111 WHITE, UNDERGROUND URANIUM WORKERS, 1950 TO 1971, BY AGE*

			Age Groups in Years													
	Total		30–39		40–49		50–59		60–69		70–79		Less than 55		55 and over	
Cell type	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)
Squamous cell carcinoma	28	25.2	0		5	18.5	12	22.6	8	36.4	3	50.0	10	19.6	18	30.0
Small cell carcinoma	67	60.4	3	100.0	20	74.1	31	58.5	12	54.5	1	16.7	38	74.5	29	48.3
Adeno-carcinoma	7	6.3	0		0		5	9.4	0		2	33.3	1	2.0	6	10.0
Other†	9	8.1	0		2	7.4	5	9.4	2	9.1	0		2	4.0	7	11.7
Total	111	100.0	3	100.0	27	100.0	53	100.0	22	100.0	6	100.0	51	100.0	60	100.0

* Adapted from Archer and associates (115) (WHO classification in 71%; autopsy, 73%).
† Includes: Large cell, 1; combined epidermoid and adenocarcinoma, 3; carcinoid, 1; double primaries: small cell and epidermoid, 1; epidermoid and small cell, 2; small cell and adenocarcinoma, 1.

workers, 1950 to 1971, describes the main sources from which tissue specimens were acquired (table 13) (115). It also relates the patterns of cell types diagnosed by a three-member panel of pathologists as well as the pattern diagnosed by a hospital pathologist in instances where tissue specimens were unavailable to the panel. Two thirds (n = 75) of the diagnoses were made by the panel and one third (n = 36) were obtained from a report by a hospital pathologist. The sources from which specimens were obtained permitted grouping into two main methods of diagnosis, i.e., autopsy series (n = 81, 73%) and biopsy series (n = 30, 27%). A clear distinction between bronchial and surgical biopsies was not presented. Small cell carcinoma was predominant (60%) and it was more pronounced in the autopsy series (67% of cell types) than in the biopsy series (43% of cell types). These proportional differences may be a reflection of the sources from which the tissue specimens were obtained. The proportion of small cell carcinoma diagnosed by the panel in the autopsy series was 74.6%, whereas the proportion of small cell carcinoma diagnosed by the hospital pathologist was 45.5%. In the biopsy series, the proportion of small cell carcinoma diagnosed by the panel was 56.3% and by the hospital pathologist, 28.6%. The higher proportion of small cell carcinoma reported by the panel compared with that reported by the hospital pathologist may be a reflection of differences in techniques, expertise, or cases examined.

TABLE 13

NUMBER AND RELATIVE FREQUENCIES OF LUNG CANCER TYPES IN 111 WHITE, UNDERGROUND URANIUM WORKERS BY METHOD OF DIAGNOSIS AND TYPE OF PATHOLOGY REVIEW*

	Type of Pathology Review					
	Three Pathologists (including author)		One Pathologist (independent of study)		Combined Reviews	
Method of Diagnosis, Lung Cancer Cell Types	(n)	(%)	(n)	(%)	(n)	(%)
Autopsy specimens						
Squamous cell	9	15.3	7	31.8	16	19.8
Small cell	44	74.6	10	45.5	54	66.7
Adenocarcinoma	3	5.1	2	9.1	5	6.2
Other†	3	5.1	3	13.6	6	7.4
Total	59	100.0	22	100.0	81	100.0
Biopsy specimens						
Squamous cell	5	31.3	7	50.0	12	40.0
Small cell	9	56.3	4	28.6	13	43.3
Adenocarcinoma	0		2	14.3	2	6.7
Other†	2	12.5	1	7.1	3	10.0
Total	16	100.0	14	100.0	30	100.0
Combined Autopsy & Biopsy Specimens						
Squamous cell	14	18.7	14	38.9	28	25.2
Small cell	53	70.7	14	38.9	67	60.4
Adenocarcinoma	3	4.0	4	11.1	7	6.3
Other†	5	6.7	4	11.1	9	8.1
Total	75	100.0	36	100.0	111	100.0

* Adapted from Archer and associates (115).
† Includes: Large cell, 1; combined epidermoid and adenocarcinoma, 3; carcinoid, 1; double primaries: small cell and epidermoid, 1; epidermoid and small cell, 2; small cell and adenocarcinoma, 1.

It is unfortunate that observer variability was not reported in the studies of the uranium miners, particularly in view of the 25% disagreement reported in earlier studies among pathologists diagnosing small cell carcinoma (75, 76). The effect of age on distributions of cell types of lung cancer requires careful attention in studies of environmental exposures inasmuch as small cell carcinoma seems to have a high proportion in young age groups, whereas squamous carcinoma has a high proportion in older age groups (table 2). Saccomanno and associates (114) attempted to address this question in their study of uranium miners; however, as noted previously, age-matching was difficult and the possible effect of age on the distribution of cell types of lung cancer in these workers is not clear. Saccomanno and associates (116) have recently observed that the proportion of small cell carcinoma among uranium miners decreased from 59% in 1960 to 22% in 1980 and that the proportion of adenocarcinoma increased with increasing WLM.

The excess for each of the cell types of lung cancer observed in the 121 uranium miners and their comparison subjects was recently estimated (117). Because uranium miners were observed to have 5.4 times the number of lung cancers expected, the total number of lung cancers in each cell type category was multiplied by 5.4 and the resulting distribution was compared with the distribution of cell types observed in the comparison group of 121 nonuranium miners. This technique of applying a relative increase to the observed distribution does nothing to clarify the histopathologic patterns of lung cancer in uranium miners.

A study of lung cancer cell types evaluated in 115 uranium miners in Czechoslo-

vakia, 1948 to 1974, revealed that the majority were small cell carcinoma (53.9%) and squamous cell carcinoma (34.8%) (118). An unspecified proportion of the specimens were unclassifiable, thus the representativeness of the series is unknown. Factors that may have affected the quality of the evaluations, e.g., quality of the tissue slides, were not described. One pathologist, not informed of the working history of the deceased and using the VALCCSG classification, reviewed all the specimens. The investigators, estimating ratios of observed to expected cell type proportions, reported that the proportions of both squamous cell and small cell carcinomas were increased by the level of cumulated radiation exposure. Adenocarcinoma was found not to be elevated in frequency, but the number was small (n = 4). Important aspects of a histopathologic study of lung cancer, such as sources of specimens, ages of patients, and validity and reliability of histopathologic diagnoses, were not included in the report.

A case series of 16 Navajo uranium miners in whom lung cancer was diagnosed, 1965 to 1979, reported the following cell types: small cell carcinoma, 5; undifferentiated carcinoma, 5; squamous cell carcinoma, 3; alveolar carcinoma or adenocarcinoma, 2; unknown, 1 (119). The average age at death was 46.1 yr and the mean value of cumulative radon exposure was 1,140 WLM. The significance of the distribution of lung cancer cell types in this case series is unclear because of the large proportion (38%) of undifferentiated or unknown cell types that, in the conclusions of the original report, were grouped with small cell carcinomas.

Among fluorspar miners with lung cancer in Newfoundland, Canada, 29 were diagnosed by sputum cytologic examination (miners refused surgical intervention) (120). Of these 29 cases, 26 (90%) were squamous cell carcinoma. This preponderance of squamous cell carcinoma is probably a reflection of the central location of this type of lung tumor. The low proportion of small cell carcinoma (7%) among this group of radon-exposed workers is unexplained.

A cohort of uranium workers in Ontario, Canada, has also been studied (121). The lack of a standard histopathologic classification among the pathologists was noted as a problem, and inclusion of terms such as anaplastic, undifferentiated, or poorly differentiated in all 3 of the 4 major cell types reported may be a reflection of this lack of standardization. In addition to classification problems, the use of general labels for reporting cell type distributions prohibits determination of a histopathologic pattern within this group of workers with lung cancer.

Atomic bomb survivors. A total of 204 cases of lung cancer (male, 136; female, 68) was identified in an autopsy series, 1961 to 1970, of survivors of the atomic bomb blasts in Hiroshima and Nagasaki (122). In males, the predominant cell type was squamous cell carcinoma (33.8%), and in females, it was adenocarcinoma (52.9%). The proportion of small cell carcinoma in males (22.8%) was about twice that in females (11.8%). Three cell types demonstrated a higher proportion in the ≥ 200 rad exposure group than in the < 1 rad exposure group: squamous cell carcinoma, small cell carcinoma, and adenocarcinoma. The difference between the 2 exposure groups was significant only for small cell carcinoma. Exposure data by cell type was not reported for 22.5% of the 204 cases of lung cancer; therefore, the representativeness of the exposure is uncertain. The proportion of lung cancer cases autopsied in the ≥ 200 rad exposure group (10%) was twice the proportion of lung cancer cases autopsied in the < 1 rad exposure group (5%). The larger proportion of lung cancer cases autopsied in the ≥ 200 rad exposure group may be of importance considering the high relative frequency of small cell carcinoma identified in the autopsy series. A review of this study noted that the excess number of cases, relative to expectation based on the < 1 rad exposure group, are too small to exclude equal increases in cell types other than small cell carcinoma (123).

Summary and Conclusions

Historically, pathologists and epidemiologists have been limited by available technology and classification systems in studies of the association of histopathologic cell types of lung cancer with environmental exposures. Prior to the 1960s, techniques used in the procurement and preparation of tissue specimens limited their quality and, hence, the accuracy of histopathologic diagnoses. It is only 15 yr since the WHO published the first international standard for histopathologic classification of lung tumors, which eliminated much of the ambiguity in earlier descriptions of cell types. Furthermore, information on environmental exposures available to epidemiologists has been severely limited in character (e.g., intensity, duration and type).

An increase in all major cell types of lung cancer, with no significant excess of a single cell type, has been associated with cigarette smoking. Different lung cancer cell types have been reported to predominate in studies of arsenic exposures. This predominance of numerous cell types may be a reflection of differences in the type and content of arsenic ores, differing histologic techniques, various sources of tissue specimens, and varying study designs. Two cell types, adenocarcinoma or small cell carcinoma, depending upon whether the source of the tissue specimens was autopsy or biopsy, were prominent in a single study of beryllium exposure.

Squamous cell carcinoma was the predominant cell type reported in a case series of workers exposed to chromates and in a case series of nickel workers. The availability of comparable tissue diagnoses for nonexposed groups, identification of sources of specimens, and environmental monitoring data would greatly enhance these studies.

Small cell carcinoma was the predominant cell type reported in 3 of the 4 published case series of workers exposed to BCME. The 2 U.S. studies included cases associated with screening programs for respiratory disease, and in one of them, age may have affected the distribution of lung cancer cell types. As noted earlier, the distribution of lung cancer cell types is affected by the source of tissue specimens. The high proportion of small cell carcinoma reported in studies of uranium workers is impressive. In one study of uranium miners, the proportion of small cell carcinomas differed by sources of tissue (autopsy versus biopsy) and by type of tissue review (panel versus hospital pathologist). This provokes the question as to what extent, if any, the distribution of lung cancer cell types in uranium miners may have been affected by these factors. The effects of age at time of diagnosis and of observer variability on lung cancer cell type distribution are unclear in studies of cell types of lung cancer in persons exposed to radioactive substances.

A predominance of adenocarcinoma was reported in 3 of the 4 studies specific to lung cancer in males exposed to asbestos. Diagnoses were based on autopsy material in 2 of these studies and, in the third study, the source of tissue specimen was "pathologic material." It is likely that an association of a single cell type of lung cancer with asbestos exposure is chiefly artifactual. Greater proportions of large cell carcinoma and adenocarcinoma were found among chemical workers exposed to polyvinyl chloride dust in a synthetic chemicals plant than in a comparison group. The significance of these findings is not clear.

Most studies associating environmental exposures with histopathologic patterns of lung cancer cell types have attempted to identify a predominance of a single cell type in order to facilitate identification of causal exposures. Evidence available for a variety of known respiratory carcinogens (tobacco smoke, asbestos, arsenic, beryllium, chromate, nickel, BCME, vinyl chloride, radon gas/radon daughters, and radiation from atomic blast) has been reviewed. Limitations as described herein, prohibit definitive conclusions and, to date, no study has unequivocally demonstrated that a specific lung cancer cell type in humans is uniquely associated with a specific physical or chemical exposure. Conversely, several investigators have concluded that an increased relative frequency of two or more lung cancer cell types occurs after certain specific exposures. It is possible that one or more lung cancer cell types may be associated with specific environmental exposures. However, in order to differentiate apparent from real associations, studies must consider the correlated factors discussed above,

which may influence proportional distributions of lung cancer cell types.

The *challenge* for researchers of this topic is to design and conduct studies that will reflect distributions of lung cancer cell types in the general population as well as cell type distributions in populations exposed to specific agents. It is necessary to establish the distribution of lung cancer cell types in the general population in order to identify any differences that may occur in other populations as a result of exposure to specific substances. The *dilemma* for researchers is how to account for the numerous factors, as outlined herein, that may impinge upon the precision and reliability of a study of lung cancer cell types in populations. The dilemma may be resolved somewhat by the following procedures: (*1*) use carefully obtained and prepared specimens for diagnosis; (*2*) ensure that qualified persons, using a standard classification, examine specimens in a way that will diminish bias, such as that associated with *a priori* knowledge of exposure and observer variation; (*3*) consider the effect of age of study subjects and sources of specimens on histopathologic distributions; (*4*) specify exposure(s) clearly; (*5*) select appropriate comparison subjects; (*6*) establish a complete follow-up of all study subjects.

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