

Changing Patterns of Lung Cancer Incidence by Histological Type

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Abstract

Using data from five registries covering 7% of the U.S. population, we investigated lung carcinoma incidence trends from 1969–86 by histological type, sex, race, age, calendar time period, and cohort year of birth. Among white men, squamous cell carcinoma was the most frequent histological type, but by the mid-1980s the age-adjusted rates were decreasing while rates of adenocarcinoma and small (oat) cell carcinoma continued to rise. Among white women, adenocarcinoma was the most frequent type, followed by small cell carcinoma, with rates of all histological types rising over the entire study period. Similar time trends were seen among blacks. Rates for squamous cell carcinoma among both sexes and adenocarcinoma among men, however, were considerably higher for blacks than whites, whereas no racial disparity was seen for small cell carcinomas. Rates for each histological type were higher among men than women, although male-female sex ratios diminished over time. Age-specific rates varied considerably by cohort year of birth; incidence of squamous cell carcinoma among men increased steadily among those born from the late 1800s to the first quarter of this century before declining among those born thereafter. Cohort peaks were also reached, although about 10 to 20 years later, for small cell carcinoma and adenocarcinoma, suggesting an eventual reduction in incidence in these histological types as well. For each type, the peak incidence occurred earlier for men than women. These differing incidence patterns add to the evidence that the mechanisms of lung carcinogenesis may vary by histological type.

Introduction

Substantial increases in overall U.S. lung cancer mortality and incidence have occurred during this century, although recent declines in rates at younger ages have been observed (1). The trends may not be uniform across the several different histological types of lung cancer, however. In particular, a disproportionate increase in incidence of adenocarcinoma has recently been reported

for several areas of the country (2–4). Using population-based data available for about 7% of the U.S. population residing in five geographic areas, we analyzed lung carcinoma incidence rates for 1969–86 by histological type according to sex, race, age, calendar time period, and cohort year of birth to discern patterns which may provide further clues regarding the etiology and prevention of these cancers.

Methods

Population-based incidence data are available from the 1969–71 Third National Cancer Survey (5), its successor the SEER² program (6), and the Connecticut Tumor Registry (7). Because the Third National Cancer Survey and the SEER program include somewhat different locales and there is geographic variation in the incidence of and trends in lung cancer (8), we restricted our analysis to the five geographic areas for which data are available over the time span 1969–86: Atlanta, Connecticut, Detroit, Iowa, and San Francisco-Oakland (9). Data are not available for all areas for the years 1972–74, so these years are omitted from the analysis. Although not a random sample, the populations in these areas comprise about 7% of the U.S. population, and lung cancer mortality trends in these five geographic areas have been shown to be very similar to those in the United States as a whole (9).

Records pertaining to cases diagnosed during the early study years were coded according to the *Manual of Tumor Nomenclature and Coding* (10) and were subsequently converted to the ICDO (11) in use more recently. Newly diagnosed invasive cases of primary carcinoma arising in the lung, bronchus, or trachea (ICDO topography codes 162.0–162.9), omitting those arising in the pleura, were selected for study. Based on morphology, the following histological categories (ICDO codes) were formed: squamous cell carcinoma (8070-6); small (oat) cell carcinoma (8041-5); bronchioloalveolar adenocarcinoma (8250-1); other adenocarcinoma (8050-2, 8140-231, 8260-550, 8570-1); adenosquamous carcinoma (8560); malignant carcinoid (8240-6); and other and unspecified carcinomas (8010-34, 8082-123). In the early years, large cell carcinomas were not distinguished in the coding system (*Manual of Tumor Nomenclature and Coding*) from carcinoma NOS; thus they are included in the “other and unspecified” category throughout. Less than 3% of the cases were not specified as some form of carcinoma and were deleted from consideration.

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² The abbreviations used are: SEER, Surveillance, Epidemiology, and End Results; ICDO, International Classification of Diseases for Oncology; NOS, not otherwise specified.

All rates are expressed per 100,000 person-years. Age-adjusted rates were calculated by the direct method with the 1970 U.S. population as the standard. Three-year time periods were used: 1969–71; 1975–77; 1978–80; 1981–83; and 1984–86 for the secular trends analysis and 1969–71; 1974–76; 1979–81; and 1984–86 for the cohort trends analysis. Average annual percentage changes were estimated by a linear regression of the logarithm of the respective rates on calendar year, weighted by the number of cases.

Results

A total of 117,116 lung carcinomas were diagnosed over the study period in the five geographic areas, with 91% microscopically confirmed. Although there was little variation by race and sex, ranging from 90% among white men to 93% among black men, the confirmation rate rose from 87% during 1969–71 to 93% during 1984–86. With the exception of cases diagnosed simply as carcinoma NOS, for whom the confirmation rate was 55%, all histological categories had microscopic confirmation rates of 98% or greater.

For all sex-race groups combined, age-adjusted incidence of total lung carcinoma increased about 3%/year, from 38.6 during 1969–71 to 58.4/100,000 person-years during 1984–86. The rate rose 25% among white men, almost 50% among black men, and 150% or more among both white and black women (Table 1). Squamous cell carcinoma rates increased 50% or less among men while more than doubling among women. Adenocarcinoma and small cell carcinoma rates doubled among men and more than tripled among women.

As a result, the histological distribution of lung carcinomas changed over time (Table 1). Squamous cell carcinomas remain the most common type among men, despite an increasingly greater proportion that are adenocarcinomas or small cell carcinomas. Among women, adenocarcinomas are the most frequent type, and rates of small cell carcinoma now exceed those of squamous cell carcinomas among whites but not blacks. Bronchioloalveolar adenocarcinoma rates have not changed greatly, whereas those for adenosquamous carcinoma rose, but both are relatively rare forms of lung carcinoma. The combined category of other and unspecified carcinoma declined among men and increased among women.

The variation in incidence rates and trends by race and sex are presented in Fig. 1. Total lung carcinoma incidence is highest and continues to increase among black men, about 3%/year. In contrast, overall rates among white men have plateaued and actually declined slightly from 1981–83 to 1984–86. Although the age-adjusted rates are considerably lower, proportional increases have been greatest among women, about 6%/year, with small racial differences.

Fig. 1 also shows that the black excess is greatest for squamous cell carcinoma, holds to a lesser extent for adenocarcinoma, but is not found for small cell carcinoma. The male excess is prominent for all histological types, although it is greatest for squamous cell carcinoma. Male-female ratios, however, for squamous and small cell carcinomas in the mid-1980s were half their values 15 years earlier; the decline in the sex ratios was less marked for adenocarcinoma.

There are striking cohort effects for total lung cancer, with mortality among men rising sharply for those born

Table 1 Lung cancer incidence trends by histological type in five geographic areas, 1969–71 to 1984–86

	1969–71		1984–86		% change
	No.	Rate ^a	No.	Rate ^a	
White males					
Squamous cell carcinoma	3,767	21.7	5,100	27.2	25
Adenocarcinoma	1,638	9.3	3,685	19.6	111
Small cell carcinoma	1,182	6.7	2,730	14.5	116
Bronchioloalveolar adenocarcinoma	285	1.6	289	1.5	-6
Adenosquamous carcinoma	58	0.3	222	1.2	300
Malignant carcinoid	36	0.2	86	0.4	100
Other and unspecified	4,630	27.5	3,669	19.7	-28
Total carcinomas	11,596	67.3	15,781	84.1	25
White females					
Squamous cell carcinoma	566	2.7	1,658	6.9	156
Adenocarcinoma	747	3.5	2,572	11.2	220
Small cell carcinoma	342	1.6	1,743	7.4	363
Bronchioloalveolar adenocarcinoma	162	0.8	314	1.3	63
Adenosquamous carcinoma	22	0.1	123	0.5	400
Malignant carcinoid	43	0.2	131	0.6	200
Other and unspecified	1,151	5.3	1,948	7.8	47
Total carcinomas	3,033	14.2	8,489	35.7	151
Black males					
Squamous cell carcinoma	543	33.8	1,070	50.6	50
Adenocarcinoma	193	11.5	633	28.9	151
Small cell carcinoma	129	8.0	330	15.2	90
Bronchioloalveolar adenocarcinoma	22	1.4	42	2.0	43
Adenosquamous carcinoma	10	0.5	37	1.7	240
Malignant carcinoid	1	0.1	10	0.4	300
Other and unspecified	463	30.8	590	28.1	-9
Total carcinomas	1,361	86.1	2,712	126.9	47
Black females					
Squamous cell carcinoma	67	3.4	291	10.5	209
Adenocarcinoma	75	3.8	340	12.2	221
Small cell carcinoma	37	1.8	190	6.8	278
Bronchioloalveolar adenocarcinoma	10	0.5	30	1.1	120
Adenosquamous carcinoma	1	<0.1	26	0.9	n/a ^b
Malignant carcinoid	1	<0.1	12	0.4	n/a
Other and unspecified	107	5.7	232	8.3	46
Total carcinomas	298	15.3	1,121	40.2	163

^a Rate per 100,000 person-years, directly age-adjusted using the 1970 U.S. standard.

^b n/a, not appropriate.

from the late 1800s and early 1900s up to about 1925–30 and then steadily declining for those born thereafter (1). Similar trends are apparent for women, although the peak mortality appears for those born about 1935–40 (1). Fig. 2 shows that cohort effects are evident in the incidence of each of the three major lung carcinoma histological types, although the patterns differ between them. Among men, the recent decline in rates at younger ages is strongest for squamous cell carcinoma; incidence peaked for those born around 1920–25 and has substan-

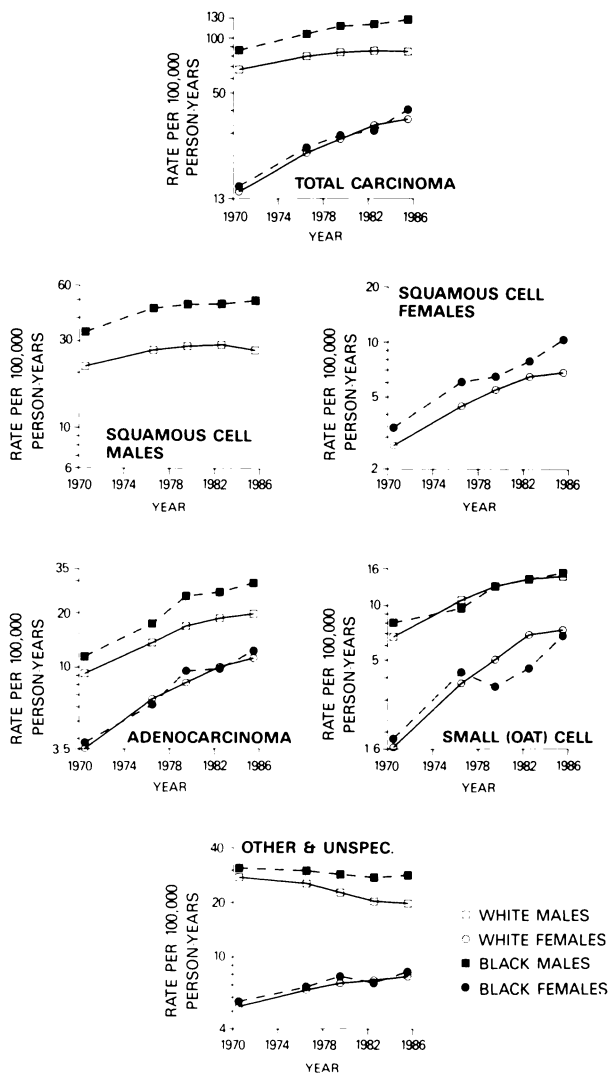


Fig. 1. Age-adjusted incidence trends in carcinoma of the lung in five geographic areas by histological type, race, and sex, 1969-71 to 1984-86.

tially declined since (the drop is most evident at ages 35-44). For small cell carcinomas, men born around 1930-35 appear at highest risk, while for adenocarcinoma the maximum occurs for men born around 1940. Rates of increase among cohorts born in the early 1900s were greater for small cell and adenocarcinoma than for squamous cell carcinoma. Among women, histological type differences seem less pronounced, with sharply rising trends for all histological types until a plateauing for those born around 1940, and perhaps somewhat earlier for squamous cell carcinoma. Within each histological type, trends in age-specific incidence were generally similar between blacks and whites.

Discussion

Our findings show that lung carcinoma incidence patterns vary by histological type. Squamous cell carcinoma remains the most frequent type among men but soon

may be replaced by adenocarcinoma, the most common type among women. Racial differences in rates (but not trends) also are prominent, with a substantial black excess for squamous cell carcinoma, higher rates in blacks only for men for adenocarcinoma, and no increased risk in blacks for small cell carcinoma. Of the three main histological types, rates of small cell carcinoma generally are increasing the most rapidly.

These trends in part may be influenced by methods of diagnosis (12-14). The histological type distribution may be affected by the source (centrally or peripherally within the lung) of the specimen and whether the specimen was obtained by cytology, biopsy, surgery, or autopsy. The introduction of the flexible bronchoscope in 1968 and the greater use of transthoracic aspiration needle biopsy of the lung over the past two decades have increasingly led to diagnoses based on small transbronchial biopsy specimens and on fine needle aspirate cytology (15). Both of these techniques have improved access to the lung periphery, which could increase the number of adenocarcinomas diagnosed without thoracotomy, since adenocarcinoma is primarily a peripheral tumor (16). In addition, new histochemical stains have been developed, improving the ability to identify small cell carcinoma that previously might have been classified as undifferentiated carcinoma and adenocarcinoma that might have been called large cell carcinoma (17, 18). The proportion of cases microscopically confirmed increased only from 87% to 93% over the study period, and the rate of change for carcinoma NOS was less than that observed for the specific histological types (and declined notably only for white men), suggesting that these diagnostic changes have not had a major impact. Secular changes in diagnostic practices may have also influenced the rates of the other histological types of lung cancer (12, 19). Large cell carcinomas were not coded separately at the outset of the study period, so we could not evaluate trends. Although these cancers may be particularly difficult to distinguish from poorly differentiated squamous cell or adenocarcinoma, large cell carcinomas were the fourth most frequent specific histological type of lung cancer in recent years. Several types may be present in the same tumor, and the composition may change over time (20). Part of the increases in adenocarcinoma may be due to improved specificity of cases previously diagnosed only as squamous cell or adenocarcinoma.

Although potentially desirable, a standardized pathologic review was not feasible for the 117,000 tumors in our study. Comparison of cases routinely reported to one of the registries of the SEER program with the judgment of a panel of two review pathologists revealed, however, generally good agreement for squamous cell carcinoma, adenocarcinoma, and small cell carcinoma, the main categories we have investigated here, but difficulties with the diagnosis of large cell carcinomas (21). Proper determination of the tumor type is important because the behavior, growth rate, and metastatic potential of lung cancer, and thus treatment decisions, are influenced by the histology (12, 16). Surgery and/or radiotherapy are the treatments for squamous cell and adenocarcinoma, whereas chemotherapy has shown success against small cell carcinoma.

Although most lung cancer is environmentally induced, it is not clear why an exposure (such as cigarette

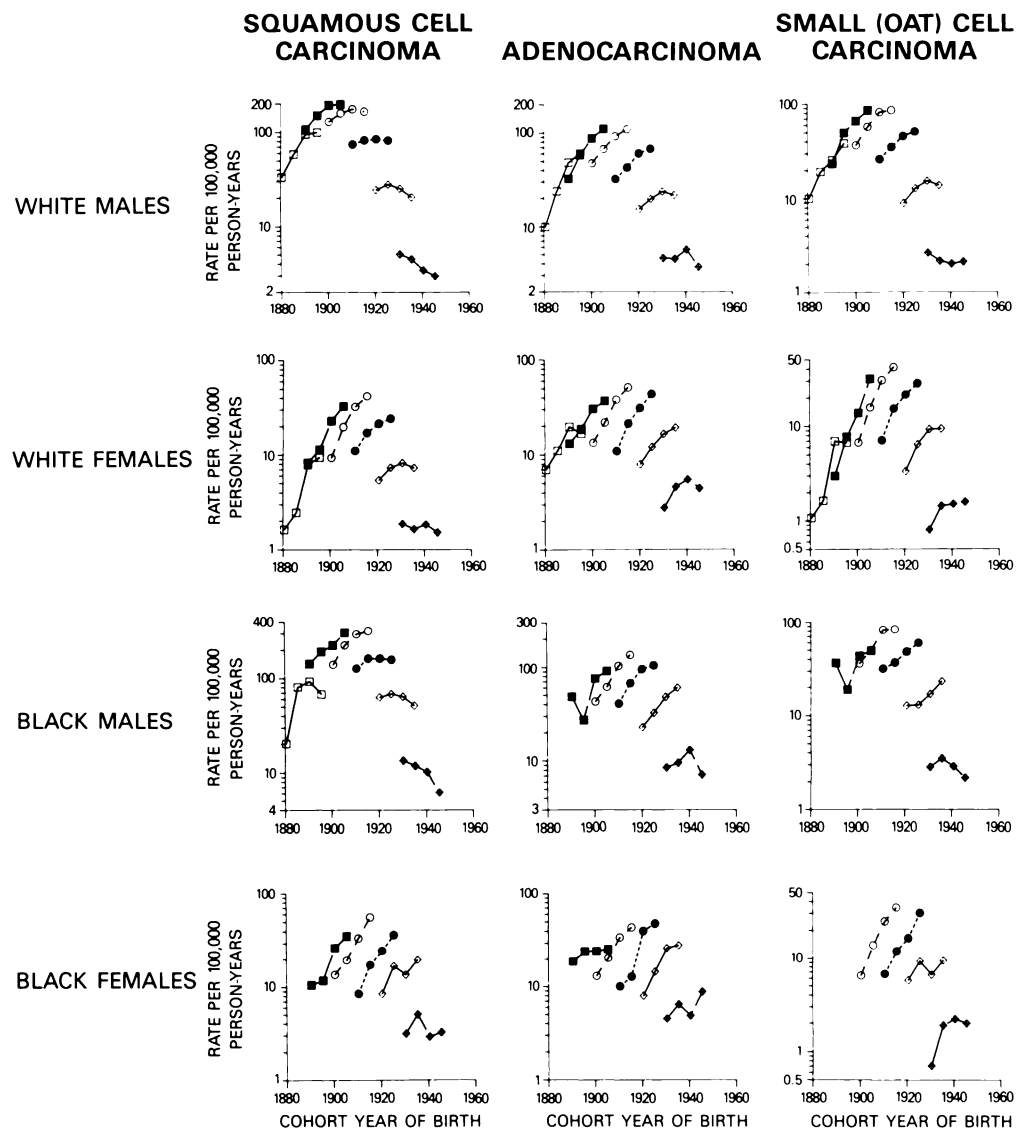


Fig. 2. Age-specific incidence trends in carcinoma of the lung by race, sex, histological type, and cohort year of birth. Note: Curves are shown only for those histological type/race/sex/age groups that had cases observed during each of the time intervals. Age: \blacklozenge , 35-44; \diamond , 45-54; \bullet , 55-64; \circ , 65-74; \blacksquare , 75-84; \square , 85+.

smoking) might lead to squamous cell carcinoma in one individual, a small cell cancer in another, and adenocarcinoma in a third. It has been postulated, but not proved, that most lung cancers arise from similar cellular origins, with a spectrum then involving transitions between differentiated adenocarcinoma or squamous cell, undifferentiated large cell, and progressively less differentiated small cell cancer (18). After a tumor is initiated, the mucous cell perhaps being the most susceptible, the phenotype which is expressed then may depend upon promoters in the microenvironment (20). One might thus expect one or more risk factors or exposures to be associated with several histological types and other factors to be more restricted in their associations.

Cigarette smoking is the dominant risk factor for lung cancer (22, 23). In the United States, the cohorts with the highest prevalence of cigarette smoking were men born during the 1920s and women born during the 1930s (22, 24); these cohorts also had the highest total lung

cancer rates (1). Whereas cigarette smoking has been associated with all three major forms of lung carcinoma, the largest relative risks are for squamous cell carcinoma and the smallest for adenocarcinoma (23, 25). The cohort patterns observed here for squamous cell carcinoma most closely follow the smoking prevalence patterns, whereas adenocarcinoma appears to peak among cohorts born 10-20 years later, at least among men. The differences suggest that smoking intensity, duration, cessation, or other characteristics of exposure to carcinogens in tobacco smoke may differentially affect the development of the various types of tumors. In the largest case-control study of lung cancer evaluating effects of smoking by histological type, risks of squamous cell carcinoma rose more sharply with duration of smoking and fell more quickly following cessation of smoking than did risks of adenocarcinoma, whereas patterns with amount smoked were similar between these histological types (25). In another study, risks also were higher and declined more

dramatically with smoking cessation for squamous and small cell carcinomas than for adenocarcinomas (26). The earlier plateau and decline in squamous cell carcinoma incidence are consistent with this histological type being more readily influenced by smoking duration and cessation, since its patterns more closely resemble downward trends in smoking prevalence of the 1970s and 1980s.

Other factors may also differentially affect the patterns by histological type. Even after adjustment for smoking, an increased risk among persons in "blue collar" professions was seen for squamous cell but not adenocarcinoma (27). Occupational exposure to certain chemicals (e.g., bischloromethyl ether) (28) and to radon (29) preferentially influences small cell carcinomas. Host factors may be particularly important for adenocarcinoma, in that immunological (30, 31) and hormonal (25, 32, 33) factors have been suggested to affect risk, and familial patterns have been noted (34). Among women, some of the world's highest rates of lung adenocarcinoma have been reported in China, which are possibly linked to long-term exposure to oil vapors generated by high-temperature cooking (32). Consumption of vegetables and fruits, especially foods containing β -carotene, appears protective for lung cancer, most notably for squamous cell carcinoma (35). However, data on trends over time in the prevalence of exposure to these other risk factors are generally unavailable for correlations with the trends in lung cancer incidence by histological type.

Other incidence surveys have documented histological differences by sex, income, tumor location, and time (2-4, 36-39). In combination, the variations observed suggest that further investigations into the etiology and prevention of lung cancer incorporate, whenever possible, information on histological type to determine whether the various forms are different manifestations of the same disease process or different diseases with perhaps some shared and some distinct risk factors.

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