ARTICLES

Cigarette Smoking and Changes in the Histopathology of Lung Cancer

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Background: **Adenocarcinoma of the lung, once considered minimally related to cigarette smoking, has become the most common type of lung cancer in the United States. The increased incidence of this cancer might be explained by advances in diagnostic technology (i.e., increased ability to perform biopsies on tumors in smaller, more distal airways), changes in cigarette design (e.g., the adoption of filtertips), or changes in smoking practices. We examined data from the Connecticut Tumor Registry and two American Cancer Society studies to explore these possibilities.** ***Methods:*** **Connecticut Tumor Registry data from 1959 through 1991 were analyzed to determine whether the increase in lung adenocarcinoma observed during that period could be best described by birth cohort effects (i.e., generational changes in cigarette smoking) or calendar period effects (i.e., diagnostic advances). Associations between cigarette smoking and death from specific types of lung cancer during the first 2 years of follow-up in Cancer Prevention Study I (CPS-I), initiated in 1959) and Cancer Prevention Study II (CPS-II, initiated in 1982) were also examined.** ***Results:*** **Adenocarcinoma incidence in Connecticut increased nearly 17-fold in women and nearly 10-fold in men from 1959 through 1991. The increases followed a clear birth cohort pattern, paralleling gender and generational changes in smoking more than diagnostic advances. Cigarette smoking became more strongly associated with death from lung adenocarcinoma in CPS-II compared with CPS-I, with relative risks of 19.0 (95% confidence interval [CI] = 8.3–47.7) for men and 8.1 (95% CI = 4.5–14.6) for women in CPS-II and 4.6 (95% CI = 1.7–12.6) for men and 1.5 (0.3–7.7) for women in CPS-I.** ***Conclusions:*** **The increase in lung adenocarcinoma since the 1950s is more consistent with changes in smoking behavior and cigarette design than with diagnostic advances. [J Natl Cancer Inst 1997;89:1580–6]**

In the late 1950s and early 1960s, Doll et al. *(1)* and Kreyberg *(2)* described the relationship between tobacco smoking and adenocarcinoma of the lung as ''slight, if any.'' Subsequent epidemiologic studies *(3–9)* consistently found smoking to be associated with adenocarcinoma, yielding relative risk (RR) estimates of 2.0–5.0. Since the association was weaker than that observed with squamous cell or small-cell lung carcinomas, it remains controversial why, in the late 1980s, adenocarcinoma became the most common lung cancer in U.S. Surveillance, Epidemiology, and End Results[1] (SEER) tumor registries *(10)*.

One hypothesis is that adenocarcinoma incidence may have increased disproportionately because diagnostic advances made it easier to perform biopsies on tumors in small, distal airways where these tumors often arise *(11)*. Rather than being missed entirely or classified as ''other'' or ''unspecified'' histology, peripheral adenocarcinomas can now be investigated without thoracotomy or autopsy. The innovations leading to this diagnostic capability were flexible bronchoscopy, introduced in 1968 *(12)*, and thin-needle aspiration *(13–16)*, computerized scans *(17)*, and improved stains for mucin, all introduced in the 1980s *(18)*. These diagnostic advances would be expected to cause discrete ''period'' increases in adenocarcinoma in the 1970s and 1980s and a disproportionate rise in incidence among the elderly, who would mostly have been excluded from diagnostic thoracotomy in the past *(11)*.

A second possible explanation is that design changes in cigarettes could actually have changed the location and histologic distribution of lung cancers for two reasons *(19)*. First the smoke from medium- and low-yield filtertip cigarettes, introduced since the 1950s, is inhaled more deeply than smoke from earlier unfiltered cigarettes *(19,20)*. Inhalation transports tobacco-specific carcinogens more distally toward the bronchoalveolar junction where adenocarcinomas often arise *(19)*. Second, blended reconstituted tobacco, introduced in the 1950s, releases higher concentrations of nitrosamines from tobacco stems than did products made predominantly from tobacco leaves *(21)*. Nitrosamines from tobacco are known to induce lung adenocarcinomas in rodents when injected systemically *(22)*.

Our analyses used several data sources to test the following: a) whether the increase in adenocarcinoma in Connecticut from

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See ''Notes'' following ''References.''

1950 through 1991 followed major diagnostic advances (calendar period increases) or gender and generational changes in smoking (birth cohort effects); b) whether the increase affected the old more than the young; and c) whether smoking became more strongly associated with death from adenocarcinoma in a large, prospective American Cancer Society (ACS) study initiated in the 1980s than in a similar study initiated in the 1960s *(23)*.

Subjects and Methods

Connecticut Tumor Registry

Lung cancer incidence and histology, but not information on individual smoking behavior, have been recorded in Connecticut for over four decades *(24)*. We identified newly diagnosed, invasive primary carcinomas of the lung, bronchus, or trachea [International Classification of Diseases for Oncology (ICD-O) topography codes 160.0–162.9 *(25)*] in Connecticut residents from 1950 through 1991. On the basis of morphology *(25,26)*, we measured trends in the incidence of squamous cell carcinoma (ICD-O codes 8070–6 and 8051–2), small-cell and oat cell carcinomas (ICD-O codes 8041–5), and adenocarcinoma (ICD-O codes 8250–1 and 8140–381) according to 5-year age and calendar time intervals and according to 10-year birth cohorts. Histologic diagnoses before 1976 were coded originally according to the Manual of Tumor Nomenclature and Coding (MOTNAC) *(27)* and were later converted to ICD-O coding *(25,28,29)*. Because MOTNAC grouped large cell carcinomas with ''carcinoma NOS (not otherwise specified)'' *(27)*, and because these tumors are classified variably by pathologists *(28)*, we did not examine large-cell carcinomas as a separate category but grouped them with ''other and unspecified'' tumors. Age-, sex-, and calendar period-specific incidence rates (per 100 000 person-years) were calculated by use of Connecticut census data *(24)*, and the rates were age adjusted by direct standardization to the 1970 U.S. population.

ACS Studies

We measured the association between cigarette smoking and death rates from adenocarcinoma, squamous cell carcinoma, and small-cell carcinoma in two large, prospective mortality studies initiated by the ACS in 1959 and 1982, i.e., Cancer Prevention Study I (CPS-I) and Cancer Prevention Study II (CPS-II), respectively, as described elsewhere *(23,30–34)*. More than 20 000 deaths occurred among the more than one million participants in each study during the first 2 years of follow-up (Table 1), the time period when histologic information on tumors was collected in both studies. Death certificates were obtained for 97.0% and 94.1% of persons known to have died in CPS-I and CPS-II, respectively. The underlying cause of death was determined from death certificates, using the criteria for lung cancer of the International Statistical Classification of Diseases, Injuries, and Causes of Death, 7th revision *(35)* codes 162–163 and 9th revision *(36)* code 162. Hospital records were sought for all cancer deaths during the entire follow-up of CPS-I and the first 2 years of follow-up of CPS-II. Microscopic or cytologic reports were available for 70.0% of lung cancer deaths in CPS-I and 61.5% in CPS-II. Cell type in CPS-I was classified according to a precursor of the 1965 edition of the Systematized Nomenclature of Pathology *(37)*, and, in CPS-II, according to ICD-O *(25)*.

At the time of enrollment, all participants completed a four page questionnaire on smoking history, current medical illnesses, and other characteristics. We excluded persons with unclassifiable or missing information on smoking, men who ever smoked pipes or cigars, former smokers (persons who reported past but not current smoking), and persons who reported lung cancer at baseline (Table 1) *(23)*. Participants in CPS-I and CPS-II were more likely to be college educated, married, middle class, and white than the U.S. general population *(38)*.

We measured death rates from lung cancer during the first 2 years of follow-up in each study according to the histologic type of tumor among persons who, at the time of enrollment, had never smoked any tobacco product and in those who currently smoked cigarettes only. Age-adjusted death rates were directly standardized to the age distribution of CPS-I and CPS-II combined. Ninety-five percent confidence intervals (CIs) around the rates were calculated by use of the methods of Breslow and Day *(39)*; CIs for the RR estimates used approximate variance formulas *(40)*.

Table 1. Selected characteristics of Cancer Prevention Study I (CPS-I) and Cancer Prevention Study II (CPS-II)

Full cohorts	CPS-I	CPS-II
Follow-up period*	1959–1961	1982–1984
Study participants, No.	1 051 038	1 185 106
Vital status, No. (%)*		
Alive	1 018 968 (97.0)	1 140 919 (96.3)
Dead	20 484 (1.9)	22 897 (1.9)
Lost to follow-up	11 586 (1.1)	21 704† (1.8)
Exclusions, No.		
Ever pipe/cigar smoker	148 828	101 600
Former cigarette smoker‡	70 108	262 790
Smoking data incomplete/ unclassified§	44 715	109 353
Lung cancer at baseline (enrollment)	137	484
Total exclusions	264 788	474 227
Analytic cohorts		
Current cigarette smoker	298 612	228 382
Lifelong nonsmoker	487 638	482 497
Total analytic cohort	786 250	710 879

*Follow-up period restricted to the first 2 years of follow-up (through September 30, 1961, for CPS-I and August 31, 1984, for CPS-II), when information on tumor histology was collected.

†This number represents the number of participants lost to follow-up during the first 6 years of CPS-II (1982–1988); the number for the period 1982–1984 is unavailable. Consequently, the numbers in this column do not sum to the total.

‡Former cigarette smokers were persons who reported past but not current smoking at study enrollment.

§Excludes subjects with incomplete or unclassifiable data on smoking status, pipe/cigar smoking, cigarettes per day, or years smoked.

Results

Connecticut Tumor Registry

The age-adjusted incidence of adenocarcinoma in Connecticut increased nearly 17-fold in women (from 0.9 to 15.2 cases per 100 000 person-years) and nearly 10-fold in men (from 2.4 to 23.2 cases per 100 000 person-years) from 1950 through 1991 (Fig. 1). The increase accelerated slightly between 1970 and 1974, but it was not confined to the intervals following diagnostic advances. Rather, adenocarcinoma surpassed squamous cell carcinoma among men and women combined in Connecticut in the 1980s for two reasons. First, its incidence continued to rise, although more slowly, beyond 1985, when squamous cell and small-cell carcinomas had begun to level off and decline. Second, women contributed a larger percentage of all lung cancers in 1990 through 1991 (39.9%) than in 1950 through 1954 (13.5%), and adenocarcinoma was the most common lung cancer cell type in women throughout the interval.

Table 2 shows that the increase in adenocarcinoma in Connecticut began by the 1950s and affected all ages from 40 to 89 years. Although the increase was proportionately larger between ages 50 and 89 years than ages 40–49 years, much of it preceded the 1970s when diagnostic innovations might be expected to enhance differentially diagnosis of adenocarcinoma in the elderly.

In birth cohort analyses (Fig. 2), the age- and sex-specific incidence of adenocarcinoma increased progressively with decade of birth from 1880–1889 to 1930–1939, peaked in 1930–1939, and began to decrease in the 1940–1949 birth cohort. The decrease in adenocarcinoma incidence among men and women

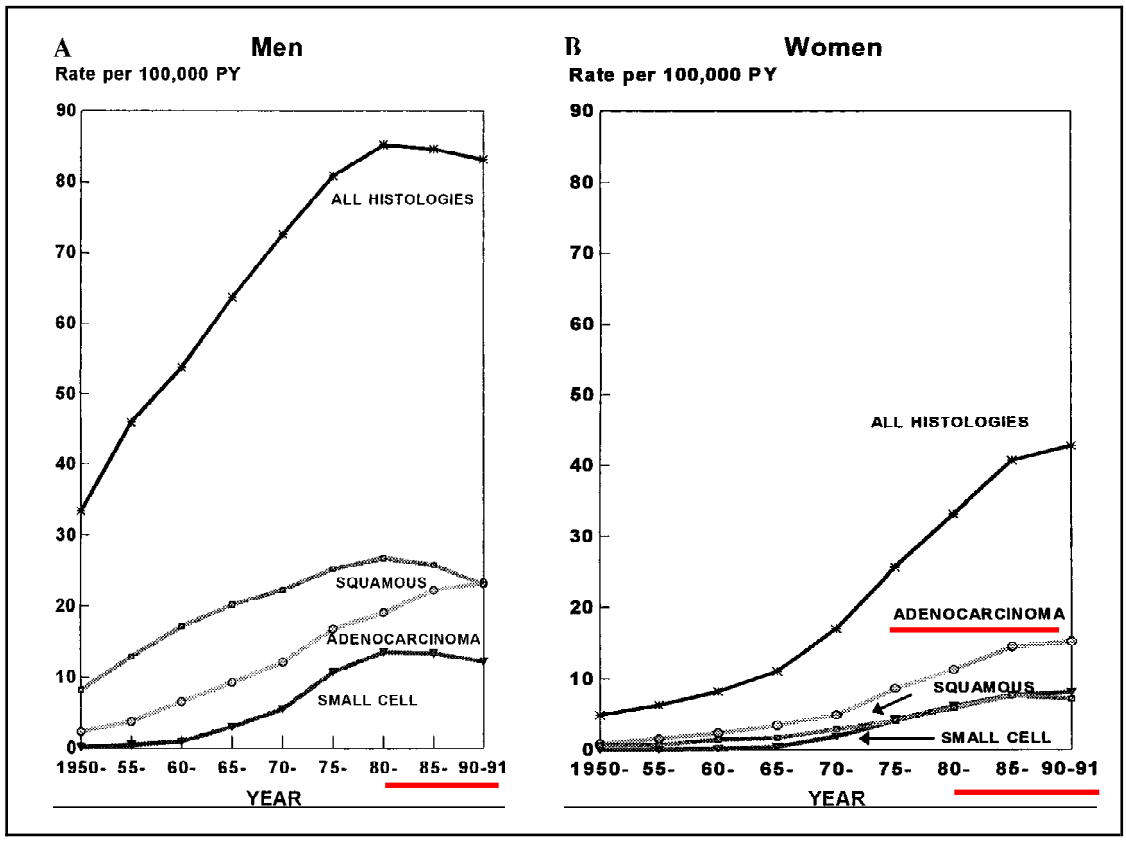

Fig. 1. Trends in the age-adjusted incidence of lung cancer according to histologic type in Connecticut, 1950 through 1991. PY = person-years; squamous = squamous cell.

born after 1939 differed in several ways from the decrease in squamous cell carcinoma (Fig. 3) and small-cell carcinoma (data not shown). First, its incidence began decreasing in the same birth cohort for men and women (1940–1949), whereas the downturn in other cell types was not synchronous across sex. Adenocarcinoma incidence peaked in men born in 1930–1939, 20 years later than squamous cell carcinoma (1910–1919 birth cohort; Fig. 3) and 10 years later than small-cell carcinoma (1920–1929 birth cohort). The birth cohort trends in small-cell carcinoma (not shown) were intermediate between those of squamous cell carcinoma and adenocarcinoma, peaking in 1920–1929 in men and 1930–1939 in women. We discuss below how these temporal progressions correspond to gender and generational changes in smoking.

Table 2. Age-specific incidence (per 100 000 person-years) of adenocarcinoma of the lung in Connecticut according to calendar period, 1950 through 1989

	Calendar period				Increase over all years
Age, y	1950–1959	1960–1969	1970–1979	1980–1989	
Men					
40–49	3.0	6.0	11.2	12.0	300%
50–59	7.9	20.4	32.7	45.2	472%
60–69	15.4	35.3	64.1	91.9	497%
70–79	11.0	41.1	80.9	122.2	1011%
80–89	9.0	17.7	47.6	88.4	882%
Women					
40–49	1.7	5.0	8.5	11.4	571%
50–59	2.7	6.6	17.6	34.4	1174%
60–69	3.8	11.2	28.2	58.5	1439%
70–79	6.2	11.3	28.0	59.4	858%
80–89	4.3	11.2	15.2	30.6	612%

ACS Studies

Lifelong nonsmokers experienced so few lung cancer deaths during the first 2 years of follow-up in the ACS studies that stable death rates could be estimated only for smokers and for adenocarcinoma in never-smoking women (Table 3). Smokers in CPS-II (1982–1984) had significantly higher death rates from adenocarcinoma than did lifelong nonsmokers. Cigarette smoking became strongly associated in CPS-II with death from adenocarcinoma (RR = 19.0; 95% CI = 8.3–47.7 in men and 8.1; 95% CI = 4.5–14.6 in women). The corresponding CPS-I estimates for adenocarcinoma were RR = 4.6; 95% CI = 1.7–12.6 in men and 1.5; 95% CI = 0.3–7.7 in women, although these estimates, as well as the association with other cell types, were unstable.

In both of the ACS studies, adenocarcinoma was the most commonly documented lung cancer histology among women, both among current smokers and among never smokers, as well as among men who had never smoked (Table 3). In CPS-II, the total number of adenocarcinoma deaths in both sexes *(143)* exceeded the number of deaths from squamous cell carcinoma *(129)*. The predominance of adenocarcinoma in CPS-II appeared to result partly from the higher death rates from this cell type among lifelong nonsmokers.

Discussion

Temporal trends in cancer histology are often difficult to study because changes in diagnosis or classification may mimic true changes in disease occurrence *(11,41,42)*. We combined several epidemiologic approaches to examine whether changes in cigarettes and smoking behavior or improved detection of

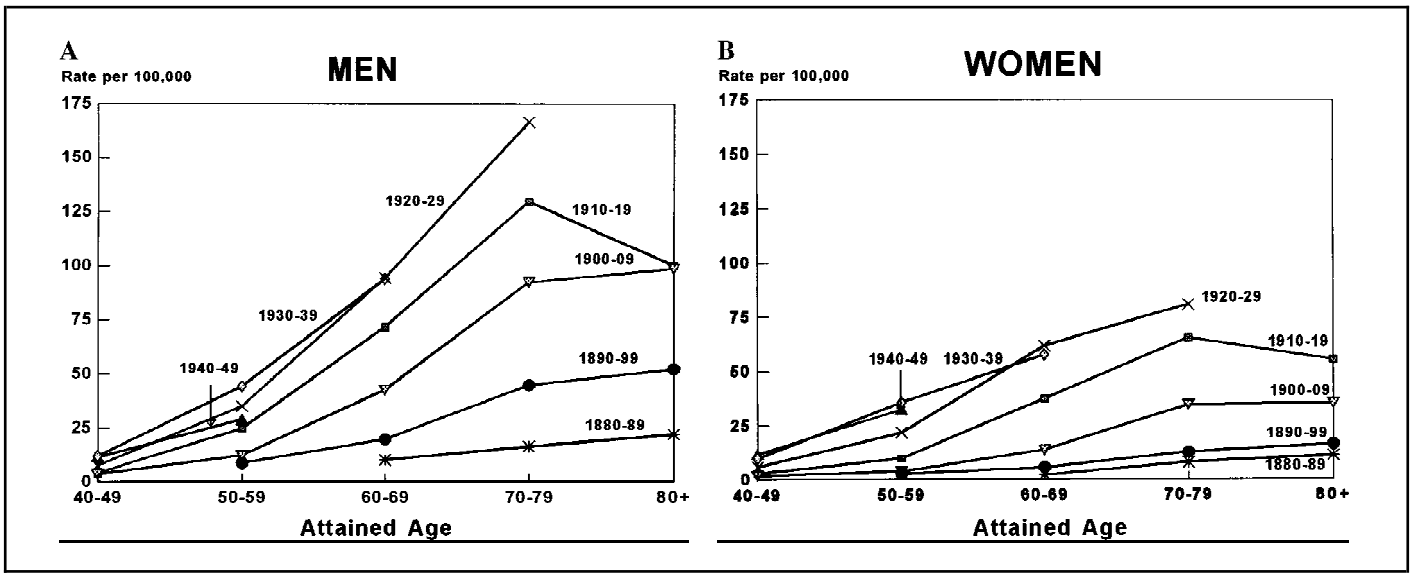

Fig. 2. Incidence of adenocarcinoma of the lung in Connecticut according to decade of birth and attained age at diagnosis. From Connecticut Tumor Registry incidence data, 1950 through 1991. Rate is per 100 000 person-years, and attained age is in years.

peripheral lung tumors better explained the increase in adenocarcinoma in U.S. adults.

Time trends in Connecticut showed little evidence that improved diagnosis or changes in disease classification were more than minor contributors to the increase in pulmonary adenocarcinoma. Neither flexible bronchoscopy nor several diagnostic innovations of the 1980s were associated with large ''period'' increases. While diagnostic advances may have contributed to the rise in incidence after 1970, they do not explain the earlier increase during the 1950s and 1960s or the decline in incidence in birth cohorts after 1939. The temporal patterns seen in Connecticut, in at least five other population-based *(9,28,43–46)* and eight hospital-based studies *(47–53)* in the United States, and in reports from Switzerland, The Netherlands, Hong Kong, Japan, Israel, and Korea *(46)* all suggest a real and international change in the histopathology of lung cancer.

The ACS studies clearly implicate smoking as the major cause of adenocarcinoma, as well as of other lung cancers. The death rates from adenocarcinoma remained low and essentially unchanged from CPS-I (1959–1961) to CPS-II (1982–1984) in lifelong nonsmokers, but they increased markedly in smokers. The apparent increase in RR between cigarette smoking and

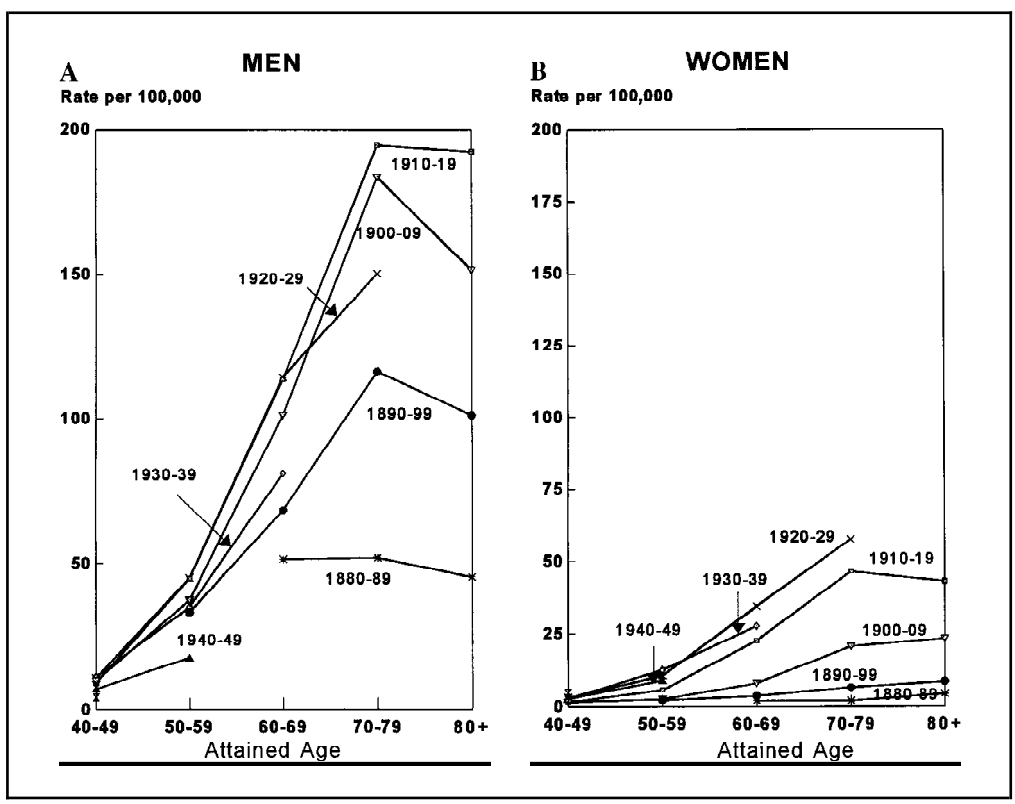

Fig. 3. Incidence of squamous cell carcinoma of the lung in Connecticut according to decade of birth and attained age at diagnosis. From Connecticut Tumor Registry incidence data, 1959 through 1991. Rate is per 100 000 person-years, and attained age is in years.

Table 3. Age-adjusted death rates from lung cancer according to histologic type and smoking status during the first 2 years of follow-up: Cancer Prevention Study I (CPS-I) and Cancer Prevention Study II (CPS-II)*

	Men				Women			
	CPS-I		CPS-II		CPS-I		CPS-II	
Person-years at risk	Nonsmoker 180 081	Smoker 274 635	Nonsmoker 252 731	Smoker 201 235	Nonsmoker 739 145	Smoker 287 220	Nonsmoker 708 413	Smoker 252 504
Histology†								
Squamous cell carcinoma								
No.	1	35	4	87	5	5	2	36
Rate‡	NC	18.2	NC	60.2	0.8	3.4	NC	21.7
(95% CI)§	—	(11.5–25.0)	—	(44.4–76.0)	(0.1–1.4)	(0.0–8.0)	—	(13.3–30.1)
Adenocarcinoma								
No.	5	23	6	79	13	4	16	42
Rate‡	3.1	14.2	2.3	44.2	1.9	NC	2.2	18.1
(95% CI)	(0.4–5.7)	(7.5–20.9)	(0.5–4.2)	(34.0–54.5)	(0.9–3.0)	—	(1.1–3.3)	(12.5–23.7)
Small-cell carcinoma								
No.	0	17	1	50	4	2	4	20
Rate‡	NC	9.8	NC	27.6	NC	NC	NC	11.5
(95% CI)	—	(4.4–15.2)	—	(19.6–35.7)	—	—	—	(5.7–17.4)

*On the basis of the first 2 years of follow-up (through September 30, 1961, for CPS-I and August 31, 1984, for CPS-II) and cigarette smoking status at enrollment. Excludes cancers prevalent at baseline.

†Histologic classification in CPS-I was based on a precursor of the Systemized Nomenclature of Pathology from the College of American Pathologists *(37)*, and, in CPS-II, on the International Classification of Diseases for Oncology (ICD-O) codes *(25)*.

‡Age-adjusted death rates (per 100 000 person-years) are directly standardized to the age distribution of the combined studies. NC = death rate not calculated because fewer than five deaths were observed.

§95% CI = 95% confidence interval.

death from adenocarcinoma in CPS-II relative to CPS-I is consistent with a trend toward higher RR estimates observed in other epidemiologic studies over time *(3–9,54,55)*. Collectively, these studies show that smoking has become more strongly associated with adenocarcinoma now than in 1962, when Kreyberg *(2)* classified adenocarcinoma as weakly related to smoking.

In addition to its growing association with cigarette smoking, adenocarcinoma is gaining prominence because of the larger contribution of women to lung cancer in the United States and the earlier and more rapid decline of squamous cell carcinoma. The latter is clearly evident among both men and women in Connecticut. Together with the ACS studies, the birth cohort trends in Connecticut also provide fairly good evidence that adenocarcinoma incidence has increased because of secular changes in cigarette smoking. Previous studies have found birth cohort patterns in smoking prevalence *(56)* and in the incidence of lung cancer and its component histologies *(28,46)*. Birth cohort trends tend to reflect etiologic factors that become fixed early in life, induce chronic disease later in life, and may evolve over several generations *(57)*. Tobacco smoking and its consequences are believed to fit birth cohort patterns because these behavioral patterns are often set in adolescence and persist through adulthood.

Our findings are weaker concerning exactly what change in cigarette smoking accounts for the change in lung cancer histology. It is intriguing that, in Connecticut, the incidence of squamous cell lung carcinoma peaked in the 1910–1919 birth cohort in men, 20 years earlier than in women (1930–1939), whereas adenocarcinoma peaked in both sexes in the 1930–1939 birth cohort. These patterns fit temporally with gender and generational differences in the type of cigarettes being smoked. Prior to the 1950s, cigarettes were predominantly unfiltered, high-tar products smoked largely by men *(58)*. The smoke from these products was too irritating to inhale deeply. Carcinogens were deposited on the epithelium at the branches of central bronchi, where squamous cell carcinomas often occur *(19)*. With the introduction of filtertip, milder cigarettes beginning in the 1950s, large numbers of both men and women began to smoke filtertip cigarettes or switched to these products *(58,59)*. The market share of filtertips increased from less than 1% in 1950 to 51% in 1960 to 80% in 1970 *(58)*. The advent of filtertip cigarettes represented less of a change for women, who were just beginning to smoke, than for men *(59)*. This circumstance may explain why, in Connecticut women, squamous cell carcinoma, small-cell carcinoma, and adenocarcinoma all peaked together in the 1930–1939 birth cohort, whereas in men, the histologic types peaked asynchronously. In contrast, any diagnostic innovations during this period would have affected men and women simultaneously.

A limitation of our study was that neither the Connecticut nor the ACS data underwent a standardized pathologic review of lung tissue. Nondifferential misclassification of disease may occur because of changing classification schemes *(11,36,60–64)*, low specificity of histologic terms *(11,63)*, and diagnostic inconsistency among pathologists *(42)*. Despite these problems, temporal comparisons of squamous cell carcinoma, small-cell carcinoma, and adenocarcinoma of the lung are thought to be valid within SEER[1] registries *(64)*. A study *(43)* in Olmsted County, Minnesota, where a single pathologist re-examined all lung cancer specimens from 1935 through 1984, found birth cohort trends almost identical to those we observed in Connecticut. One advantage of prolonged, continuous surveillance, as has occurred in Connecticut and Olmsted County *(43)*, is that it provides a continuous record of human experience in a defined geographic area over decades.

In summary, the increase in adenocarcinoma in the United States since 1950 corresponds temporally with changes in smoking behavior and in cigarette design rather than with diagnostic

advances. Adenocarcinoma is now strongly related to cigarette smoking.

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Notes

[1]*Editor's note:* SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.

We thank Stacy Adams, Heidi Miracle-McMahill, and Jane Henley for their helpful suggestions during the development of this manuscript and Audrey Earles for its preparation.

Manuscript received May 30, 1997; revised August 4, 1997; accepted September 2, 1997.