Cigarette Smoking and Changes in the Histopathology of Lung Cancer


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 filter tips), 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]
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 (27).

**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, bronchi, 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 revision using the criteria for lung cancer of the International Statistical Classification of Diseases for Oncology (ICD-O) (25). 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 revision using the criteria for lung cancer of the International Statistical Classification of Diseases for Oncology (ICD-O) (25,26). 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).
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.

### 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
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. 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.](https://academic.oup.com/jnci/article-lookup/doi/10.1093/jnci/89.21.1578)

![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.](https://academic.oup.com/jnci/article-lookup/doi/10.1093/jnci/89.21.1578)
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 changes in cigarette smoking account for the change in lung cancer history. The smoke from high-tar 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 SEER1 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

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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)*

<table>
<thead>
<tr>
<th>Person-years at risk</th>
<th>Histology†</th>
<th>Cigarette Smoking Status</th>
<th>Histology†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Squamous cell carcinoma</td>
<td>Nonsmoker</td>
<td>Smoker</td>
</tr>
<tr>
<td>No.</td>
<td>1</td>
<td>35</td>
<td>4</td>
</tr>
<tr>
<td>Rate‡ (95% CI)§</td>
<td>NC</td>
<td>18.2</td>
<td>NC</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>3.1</td>
<td>14.2</td>
<td>13</td>
</tr>
<tr>
<td>Small-cell carcinoma</td>
<td>(0.4–5.7)</td>
<td>(7.5–20.9)</td>
<td>(0.5–4.2)</td>
</tr>
<tr>
<td>No.</td>
<td>0</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Rate‡ (95% CI)§</td>
<td>NC</td>
<td>9.8</td>
<td>NC</td>
</tr>
<tr>
<td></td>
<td>(4.4–15.2)</td>
<td>(19.6–35.7)</td>
<td>—</td>
</tr>
</tbody>
</table>

*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.
advances. Adenocarcinoma is now strongly related to cigarette smoking.

References

49. el-Torky M, el-Zeky F, Hall JC. Significant changes in the distribution of cigarette smoking.


Notes

1Editor’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.

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