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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