Smoking and Adrenal Cancer Mortality among United States Veterans

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Abstract
Adrenal cancer is a rare and heterogenous group of tumors the etiology of which is largely unknown. Tobacco use was suggested as a potential risk factor in a recent case-control study of adults dying from adrenal cancers, most of which were adrenocortical carcinomas. In a cohort study of nearly 250,000 United States veterans whose mortality was followed for up to 26 years, we evaluated the risk of adrenal cancer associated with tobacco use. Relative risks and corresponding 95% confidence intervals were calculated. A total of 27 adrenal cancer deaths were observed during the follow-up period. Relative to nonusers of any tobacco, risk was elevated 5-fold (relative risk = 5.1; confidence interval = 1.1–22.4) among current cigarette smokers, with risks further increased among those who smoked >20 cigarettes/day (P for trend < 0.01). Nonsignificant increases in risk occurred among smokers of other forms of tobacco. This cohort study provides support for an etiological relationship between tobacco smoking and adrenal cancer, although further confirmatory studies are needed.

Introduction
Cancers of the adrenal gland are extremely rare tumors arising from either the adrenal cortex (adrenocortical carcinoma) or the medulla (malignant pheochromocytoma and neuroblastoma). Among adults ages 25 years and older, adrenocortical carcinoma is the major histological type, comprising nearly 90% of adrenal cancers (1). Although risk factors for these tumors are largely unknown, an excess risk was linked to cigarette smoking among men in a recent case-control study (2). To further clarify the association with cigarette smoking, adrenal cancer mortality was evaluated in a cohort of United States veterans who were followed for up to 26 years.

Materials and Methods
Detailed description of the cohort and methods of follow-up have been presented elsewhere (3–6). Briefly, the cohort comprised over 290,000 United States veterans who served in the Armed Forces between 1917 and 1940 and held active United States Government life insurance policies in 1953. Over 99.5% of policy holders were men, and nearly all were white. Information on tobacco use, including current and past smoking status, type of tobacco used, amount of current tobacco use, and age at starting to smoke, was obtained from mailed questionnaires in 1954 and in 1957 for those nonrespondent to the first mailings. Duration of smoking was estimated by the difference between age at 1954 or 1957 and the age at which the participant began smoking. No additional information on tobacco use has been collected since the initial mailings.

This study included 248,046 veterans (84% of the cohort) who responded to the questionnaires. Ascertainment of mortality of cohort members through September 30, 1980 was about 96% complete. Death certificates were obtained for 95% of the deceased veterans. Causes of death were coded using the 7th Revision of the International Statistical Classification of Diseases (7). Because of its rarity, adrenal cancer was not examined in earlier reports on this cohort (3–6). In the present analysis, the associations between adrenal cancer and tobacco use were assessed by RRs and corresponding 95% CIs, using a Poisson regression program for modeling hazard functions with grouped data (8). RRs were adjusted for age and calendar time periods in 5-year intervals.

Results
Adrenal cancer deaths were reported in 27 cohort respondents during the study period. Risk was elevated 5-fold (RR = 5.1; CI = 1.1–22.4) among current smokers (in 1954 or 1957) relative to nonusers of any tobacco (Table 1). In addition, nonsignificant excess risks of 3-fold or greater were observed among former cigarette smokers, smokers of cigars/pipes only, and "other" smokers, most of whom were former cigarette smokers who currently smoked cigars/pipes.

Among current cigarette smokers, the risk of adrenal cancer increased significantly with number of cigarettes smoked/day, although the dose-response trend (P < 0.01) was not smooth (Table 2). The risk was greater than 8-fold (RR = 8.4; CI = 1.8–39.9) for men who smoked >20 cigarettes/day. No trend was observed for age started or duration of smoking.

Discussion
The 3-fold or greater excess risks of adrenal cancer among tobacco smokers in our cohort mortality study are higher than those reported in a recent exploratory death certificate-based case-control study (2) in which controls might have smoked more than the general population. Although the small number of cases may result in risk estimates that are somewhat unstable, it is possible that the risks of adrenal cancers associated with cigarette smoking are underestimated in our study due to the misclassification of some ex-smokers as current smokers. If the smoking patterns in this
Table 1  RRs and 95% CIs of adrenal cancer and tobacco use among United States veterans, 1954–1980

<table>
<thead>
<tr>
<th>Smoking categories</th>
<th>No. of Deaths</th>
<th>Person-</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of cases</td>
<td>27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never any tobacco</td>
<td>27</td>
<td>1,064,337</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Cigars/pipes only</td>
<td>3</td>
<td>407,625</td>
<td>3.7</td>
<td>0.6-22.1</td>
</tr>
<tr>
<td>Other smokers</td>
<td>4</td>
<td>658,478</td>
<td>3.1</td>
<td>0.6-17.2</td>
</tr>
<tr>
<td>Former cigarette smokers</td>
<td>4</td>
<td>743,281</td>
<td>2.9</td>
<td>0.5-15.8</td>
</tr>
<tr>
<td>Current cigarette smokers</td>
<td>14</td>
<td>1,657,270</td>
<td>5.1</td>
<td>1.1-22.4</td>
</tr>
</tbody>
</table>

a Adjusted for age and calendar time period.
b Smokers who did not fit into one of the other categories, mostly former cigarette smokers who currently smoked cigars/pipes.
c Included cigarette smokers who also used cigars or pipes.

Table 2  RRs and 95% CIs of adrenal cancer in relation to amount and duration of smoking and age at starting smoking among current smokers

<table>
<thead>
<tr>
<th>Smoking variables</th>
<th>No. of Deaths</th>
<th>Person-</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cigarettes/day</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;10</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&gt;20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at starting smoking (yrs)</td>
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<td></td>
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<tr>
<td>&lt;16</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>&lt;24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of smoking (yrs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&gt;10</td>
<td></td>
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</tr>
</tbody>
</table>

a RR adjusted for age and calendar time period.
b RR adjusted for age, calendar time period, and number of cigarettes smoked/day.

cohort of veterans resemble those of American men in general, >40% of those smoking in 1954 or 1957 may have stopped smoking during the 26 years of follow-up (9). Furthermore, the misclassification in duration of smoking may have impeded detection of a dose-response relation.

Another limitation of our cohort study is that medical records were not obtained for histological confirmation of the adrenal cancers. However, because all of our study subjects were adults (mean age, 68 years; median age, 69 years), about 90% of the cases probably had adrenocortical carcinoma (1). Therefore, the results would not be generalizable to the less common forms of adrenal cancer during adult life, such as pheochromocytoma and neuroblastoma. Another concern is that adrenal glands are common sites of metastasis for lung cancer (10), a malignancy which is strongly linked to smoking. It is possible that the association with tobacco use observed in our study was due to misreporting of lung cancer as adrenal cancer deaths. However, given that lung cancer is a common cancer and its link with smoking is well known, whereas adrenal cancer is a rare tumor the etiology of which is largely unknown, it may be reasonable to assume that smokers who died of a possible lung or adrenal cancer would be more likely to be recorded as deaths due to lung cancer. The extent of underreporting of adrenal cancer on death certificates is unclear, although the completeness of reporting should be enhanced by the poor prognosis of this malignancy (11). If adrenal cancer decedents were more likely to be smokers than cases who survived or died of other causes, the risks associated with tobacco use would be overestimated in our study.

Experimental data evaluating the effects of smoking on the adrenal glands are limited. In an inhalation study, 3 adrenocortical carcinomas and 1 adenoma developed in 4 of 80 rats exposed to chronic cigarette smoke, but none occurred among the 93 controls (11). Although adrenal tumors have not been induced by tobacco-specific nitrosamines (12), an increased number of adrenocortical tumor foci and nodules has been found in rats given other N-nitroso compounds (13).

In summary, this cohort study of United States veterans provides support for a role of tobacco smoking in the etiology of adrenal cancer among men. Additional confirmatory analytic studies are needed to clarify the association observed with smoking by histological type and to identify possible interactions with other environmental and host factors.

References
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