Relative and Absolute Risks of Cigarette Smoking on Major Histologic Types of Lung Cancer in Korean Men

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Abstract

Objectives: Most prospective cohort studies of lung cancer focus on the relative risk rather than the absolute risk of smoking.

Methods: This prospective study included 437,976 Korean men (cohort for the National Health Insurance Cooperation Study), ≥40 years old, who were free of cancer and smoking-related chronic disease at the time of enrollment. Based on new incidence cases, relative risk and excess risk, and their 95% confidence intervals (95% CI), were estimated with the standard Poisson regression model after adjustment for age or other demographic factors and other confounders.

Results: During the 6-year follow-up period of 3,142,451 person-years, 1,357 new lung cancer cases were identified. Based on the multivariate-adjusted relative risk for current smokers, the strongest association with smoking was shown for small-cell lung cancer (relative risk, 21.7; 95% CI, 8.0-58.5) followed by squamous cell carcinoma (relative risk, 11.7; 95% CI, 7.1-19.4) and then adenocarcinoma (relative risk, 2.1; 95% CI, 1.6-2.7). In current smokers with ≥40 pack-years of exposure, excess risk was highest for squamous cell carcinoma (excess risk, 33.8; 95% CI, 10.2-109.8) followed by adenocarcinoma (excess risk, 26.7; 95% CI, 10.3-64.4), and then small-cell carcinoma (excess risk, 16.3; 95% CI, 1.8-144.3).

Conclusions: In Korean men, cigarette smoking was as important a risk factor for adenocarcinoma as it was for squamous cell and small-cell lung cancer. (Cancer Epidemiol Biomarkers Prev 2005;14(9):2125–30)

Introduction

Lung cancer is the most prevalent lethal cancer worldwide, largely due to smoking (1–4). In most populations, the proportion of lung adenocarcinomas has been increasing relative to squamous cell and small-cell carcinoma (5–11), a trend that reflects changes in smoking behavior and cigarette design (5–8, 12–14). Smoking is associated with all three types of lung cancer, but most studies suggest that the association with adenocarcinoma is weakest (1–3, 14–21). Nearly all the data, however, come from case-control studies (1, 2, 14, 16–18, 20), and prospective cohort studies generally include few non-smokers who develop lung cancer (3, 15, 17, 21). Furthermore, the studies focused on relative risk rather than absolute risk. Thus, more prospective cohort studies are needed to define the absolute risk of lung cancer attributable to smoking.

In this prospective study of Korean men, we evaluated risk estimates of smoking on the three major histologic types of lung cancer using age-adjusted incidence rate, relative risk, population-attributable risk, and excess risk.

Materials and Methods

Study Population. The Korean National Health Insurance Corporation has provided health insurance to government employees and teachers along with biennial health examinations that include height, weight, and blood pressure measurements; chest radiography; urinalysis; blood counts; and blood chemistries. In addition, a self-administered questionnaire collects information regarding medical history, current health status, family history, tobacco and alcohol consumption, dietary preferences, and leisure-time physical activity.

The study subjects derived from 1,216,041 (901,979 male and 314,062 female) government employees and teachers ≥20 years old who participated in a national health examination program begun in 1996 and constituted the cohort for the National Health Insurance Cooperation Study. They consisted of managers and professionals (0.88%), skilled workers and service workers (20.5%), plant and machine operators, (31.3%), and elementary occupations (48.3%). They were not exposed to known lung carcinogens.

They were followed-up for 6 years. We included in this analysis 454,272 men ages ≥40 years. We excluded 2,958 patients who had cancer at enrollment, men <40 years of age (because of the age distribution of lung cancer incidence), and women because their smoking rate was too low (former smokers, 2.8%; current smokers, 2.0%). We restricted our analysis to 437,976 men who provided complete information on smoking.

The incident cancer cases were identified from the Korea Central Cancer Registry, which is a nationwide hospital-based cancer registry system that includes 94% of the university hospitals and 96% of the resident training hospitals of the country (22). Using a standardized manual based on the International Classification of Disease for Oncology, professionally trained abstractors collected all relevant data from pathology reports and hospital discharge summaries (23). We identified lung cancer cases by linkage of the unique identification numbers assigned at birth to the Korea Central Cancer Registry, and we gathered mortality data by linkage to the National Statistical Office. In this study, we used only incident lung cancer cases, not the death rate data. The cases were counted based on time of diagnosis of cancer. We followed subjects without cancer up to December 31, 2002, and defined the follow-up period for each cancer case as the time...
Classification of Smoking Status. Smoking status was classified as current, former, or never smoker on the basis of the response to the following questions on the 1996 baseline questionnaire: Smoking status was classified as current, former, or never smoker on the basis of the response to the following questions on the 1996 baseline questionnaire: “Do you smoke cigarettes now?” (never/had smoked but quit/yes), “How many cigarettes per day do you smoke?” (<0.5 pack/0.5-1 pack/1-2 packs/≥2 packs), and “How many years have you smoked in your lifetime?” In Korea, as in many other countries, cigarettes are sold in packages of 20. Current smokers were subdivided into groups according to pack-years of cigarette smoking (under 20, 20-29, 30-39, 40 or over). This was not done for former smokers because the data were incomplete or missing.

Table 1. Baseline characteristics of the study population and subjects who developed lung cancer

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>All subjects N = 454,272; PY = 3,142,451, n (%)</th>
<th>Subjects who developed lung cancer</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>256,999 (56.6)</td>
<td>92 (19.6)</td>
<td>46 (21.5)</td>
</tr>
<tr>
<td>50-59</td>
<td>166,829 (26.7)</td>
<td>279 (59.5)</td>
<td>247 (53.1)</td>
</tr>
<tr>
<td>≥60</td>
<td>30,444 (6.7)</td>
<td>98 (20.9)</td>
<td>99 (21.3)</td>
</tr>
<tr>
<td>Job</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White collar</td>
<td>100,652 (22.2)</td>
<td>88 (18.8)</td>
<td>98 (21.1)</td>
</tr>
<tr>
<td>Blue collar</td>
<td>353,620 (77.8)</td>
<td>381 (81.2)</td>
<td>367 (78.9)</td>
</tr>
<tr>
<td>Place of residence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>City</td>
<td>210,613 (46.3)</td>
<td>200 (42.6)</td>
<td>227 (48.8)</td>
</tr>
<tr>
<td>Town</td>
<td>158,498 (34.9)</td>
<td>148 (31.6)</td>
<td>144 (31.0)</td>
</tr>
<tr>
<td>Country</td>
<td>85,418 (18.8)</td>
<td>121 (25.8)</td>
<td>94 (20.2)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>99,477 (22.7)</td>
<td>16 (3.6)</td>
<td>69 (15.4)</td>
</tr>
<tr>
<td>Former</td>
<td>110,293 (25.2)</td>
<td>99 (20.5)</td>
<td>92 (20.5)</td>
</tr>
<tr>
<td>Current</td>
<td>228,206 (52.1)</td>
<td>376 (83.3)</td>
<td>288 (64.1)</td>
</tr>
<tr>
<td>Years of current smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>15,732 (7.1)</td>
<td>12 (3.3)</td>
<td>10 (3.7)</td>
</tr>
<tr>
<td>10-20</td>
<td>55,658 (25.3)</td>
<td>38 (10.6)</td>
<td>32 (11.8)</td>
</tr>
<tr>
<td>20-30</td>
<td>100,524 (45.7)</td>
<td>121 (33.6)</td>
<td>95 (35.1)</td>
</tr>
<tr>
<td>≥30</td>
<td>48,206 (21.9)</td>
<td>189 (52.5)</td>
<td>134 (49.4)</td>
</tr>
<tr>
<td>Amount of current smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>37,486 (16.5)</td>
<td>28 (7.5)</td>
<td>34 (11.8)</td>
</tr>
<tr>
<td>10-20</td>
<td>186,043 (81.8)</td>
<td>332 (89.0)</td>
<td>246 (85.4)</td>
</tr>
<tr>
<td>≥20</td>
<td>5,798 (1.7)</td>
<td>13 (3.5)</td>
<td>8 (2.8)</td>
</tr>
<tr>
<td>Alcohol consumption (g/wk)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>67,578 (15.3)</td>
<td>77 (17.2)</td>
<td>85 (18.9)</td>
</tr>
<tr>
<td>&lt;51.8</td>
<td>79,820 (18.0)</td>
<td>68 (15.2)</td>
<td>91 (20.2)</td>
</tr>
<tr>
<td>51.8-124.2</td>
<td>118,707 (26.8)</td>
<td>103 (23.0)</td>
<td>106 (23.5)</td>
</tr>
<tr>
<td>124.2-289.8</td>
<td>130,841 (29.5)</td>
<td>148 (33.1)</td>
<td>118 (26.1)</td>
</tr>
<tr>
<td>≥289.8</td>
<td>46,040 (10.4)</td>
<td>51 (11.5)</td>
<td>51 (11.3)</td>
</tr>
<tr>
<td>Leisure-time physical activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>261,386 (58.7)</td>
<td>289 (64.6)</td>
<td>275 (61.2)</td>
</tr>
<tr>
<td>Moderate</td>
<td>150,754 (33.8)</td>
<td>119 (26.6)</td>
<td>150 (33.4)</td>
</tr>
<tr>
<td>High</td>
<td>33,584 (7.3)</td>
<td>39 (8.8)</td>
<td>24 (5.4)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>312,549 (68.8)</td>
<td>357 (76.1)</td>
<td>342 (73.5)</td>
</tr>
<tr>
<td>25-30</td>
<td>323,503 (29.9)</td>
<td>105 (22.4)</td>
<td>116 (25.0)</td>
</tr>
<tr>
<td>≥30</td>
<td>29,435 (1.3)</td>
<td>7 (1.5)</td>
<td>7 (1.5)</td>
</tr>
<tr>
<td>Diet preference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vegetables</td>
<td>94,982 (21.2)</td>
<td>86 (19.0)</td>
<td>101 (22.0)</td>
</tr>
<tr>
<td>Mixed</td>
<td>323,503 (72.4)</td>
<td>327 (72.4)</td>
<td>323 (70.4)</td>
</tr>
<tr>
<td>Meats</td>
<td>29,435 (6.6)</td>
<td>39 (8.6)</td>
<td>35 (7.6)</td>
</tr>
</tbody>
</table>

Abbreviations: PY, person-years; BMI, body mass index.

*Comparison among four lung cancer subgroups using Mantel-Haenszel χ² test.

†Number of cigarettes per day.

Statistical Methods. In descriptive analysis, we compared the frequency distribution of each variable across histologic type and smoking status using χ² tests.

We calculated the age-adjusted incidence rates per 100,000 person-years for each histologic type of lung cancer according to smoking status at baseline. We estimated the adjusted relative risk and 95% confidence intervals (95% CI) for current and former smokers compared with never smokers, adjusting first for age at enrollment and then for body mass index, leisure time physical activity, alcohol consumption, and preference for vegetables versus meats. We calculated excess risk, using the absolute number of smoking-induced lung cancer cases in each histologic type. We used a standard Poison regression model, which is suitable for estimating the rate of rare diseases, such as cancer, with a log link function to estimate incidence, relative risk, and excess risk.

We calculated population attributable risk (24) to estimate the significant potential public health impact of smoking on lung cancer. For that, we used the smoking prevalence data of the 1995 Korea National Statistical Office, which reported 73.0% of men as current smokers, 14.6% as former smokers, and 12.4% as never smokers (25).
Table 2. Association of selected lung cancer risk factors by smoking status

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Never, n (%)</th>
<th>Former, n (%)</th>
<th>Current, n (%)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-49</td>
<td>33 (30.0)</td>
<td>40 (17.6)</td>
<td>216 (22.2)</td>
<td>0.56</td>
</tr>
<tr>
<td>50-59</td>
<td>51 (46.4)</td>
<td>130 (57.0)</td>
<td>567 (58.2)</td>
<td></td>
</tr>
<tr>
<td>60+</td>
<td>26 (23.6)</td>
<td>58 (25.4)</td>
<td>191 (19.6)</td>
<td></td>
</tr>
</tbody>
</table>

Job

White collar 24 (21.8) 46 (20.2) 194 (19.9) 0.67
Blue collar 86 (78.2) 182 (79.8) 780 (80.1)

Place of residence

City 56 (50.9) 120 (52.6) 433 (44.4) 0.03
Town 34 (30.9) 65 (28.5) 319 (32.8)
Country 20 (18.2) 43 (18.9) 222 (22.8)

Alcohol consumption (g/wk)

0 32 (29.0) 40 (18.2) 155 (16.3) 0.0018
<51.8 21 (19.1) 37 (16.8) 158 (16.6)
51.8-124.1 21 (19.1) 54 (24.6) 225 (23.6)
124.2-289.8 29 (26.4) 61 (27.7) 301 (31.5)
>289.8 7 (6.4) 28 (12.7) 114 (12.0)

Body mass index

<25 81 (73.6) 155 (68.0) 744 (76.4) 0.14
25-30 28 (25.5) 70 (30.7) 214 (22.0)
>30 1 (0.9) 3 (1.3) 16 (1.6)

Leisure-time physical activity

Low 65 (60.8) 135 (60.8) 627 (65.7) 0.34
Moderate 63 (33.6) 71 (32.0) 260 (27.2)
High 6 (5.6) 16 (7.2) 68 (7.1)

Diet preference

Vegetable 21 (19.3) 51 (22.9) 200 (20.6) 0.24
Mixed 83 (76.1) 162 (72.6) 687 (70.9)
Meat 5 (4.6) 10 (4.5) 82 (8.5)

*Mantel-Haenszel χ² test.

In the multivariate-adjusted model, we analyzed age at enrollment, body mass index (grouped according to WHO criteria; ref. 26), leisure time physical activity (“low” for physical activity four times per week for under 30 minutes each time; “moderate” for over five times per week for under 30 minutes each time or over twice per week for over 30 minutes each time; and “high” for over five times per week for over 30 minutes each time), alcohol consumption, and preference for vegetables versus meats (Table 1).

All statistical tests were two sided and done with SAS statistical package version 8.1 (27).

Results

Baseline Characteristics. Compared with the whole study population, the proportion of subjects >50 years old and the proportion of current smokers were relatively high in subjects who developed lung cancer. In current smokers, the proportion of heavy smokers (>20 cigarette per day) and long-term smokers (>30 years) were also high.

Smoking status—but not smoking amount, duration, or any other lung cancer risk factor—differed significantly among the histologic types of lung cancer. Among the adenocarcinoma patients, 15% were never smokers in contrast to 3.6% of squamous cell carcinoma patients and 1.9% of small-cell carcinoma patients (Table 1).

Subjects who smoked were more likely than never smokers to drink alcohol and to live in a rural area. The distribution of other characteristics in lung cancer patients was similar across smoking status (Table 2).

Smoking Status and Cancer Risk. The risk of lung cancer increased from never or former to current smokers. For current smokers, all three risk measures (rate, relative risk, and excess risk) revealed a strong positive dose-response relationship between pack-years and each histologic subtype (Table 3).

Incidence Rate. During the 6 years of follow-up (3,142,451 person-years), 1,357 new lung cancer cases were reported: 469 squamous cell carcinomas, 465 adenocarcinomas, 214 small-cell carcinomas, and 209 others. Within each histologic subtype, age-adjusted incidence rate increased with increased smoking. For all three smoking categories, the incidence rate was highest for adenocarcinomas—and to a remarkable extent in never smokers (Table 3).

The age-specific incidence rate for all histologic types increased significantly with age for former smokers and more precipitously for current smokers (Fig. 1). For never smokers, however, the incidence rate for squamous and small-cell carcinoma remained relatively stable with increasing age, whereas the incidence rate for adenocarcinoma increased substantially with age, reaching almost 30 in the group >60 years.

Relative Risk. Using the relative risks estimates, we identified the significant hazard effect of smoking for each histologic type of lung cancer in former and current smokers at each exposure level (except for the relative risk of adenocarcinoma in former smokers). Small-cell lung cancer showed the strongest association with smoking, followed by squamous cell carcinoma, then others, and finally adenocarcinoma. All associations were statistically significant. It is noteworthy that the association of smoking with adenocarcinoma was the lowest, although its incidence rate was the highest in every category of smoking status and smoking amount. This pattern was similar for age-specific relative risk (data not shown). The lower relative risks for adenocarcinoma were due mainly to its high incidence rate among never smokers (11.1) compared with squamous (1.9) and small-cell (0.5) carcinomas, and other types (0.9).

Population Attributable Risk. Multivariate-adjusted population attributable risk was highest for small-cell carcinoma (93.8; 95% CI, 83.6-97.7), intermediate for squamous cell carcinoma (88.7; 95% CI, 81.7-93.1) and other subtypes (62.7; 95% CI, 42.2-75.4), and lowest for adenocarcinoma (44.5, 95% CI: 30.5-55.4). For all histologic types, smoking represented the most important and avoidable risk factor, but we did not factor in passive smoking.

Excess Risk. Given the wide variation in the incidence rate of lung cancer subtypes among never smokers, we calculated excess risk—an absolute measure of risk increase—by pack-year exposure increments (Table 3). In former smokers, the excess risk was slightly increased for all histologic types. In current smokers, the highest excess risk at all four exposure levels was for squamous cell carcinoma, and for those exposed to >20 pack-years, the excess risk for adenocarcinoma was higher than for small-cell carcinoma. At ≥40 pack-years, the multivariate-adjusted excess risk for developing squamous cell carcinoma was 33.8 compared with 26.7 for adenocarcinoma, 16.3 for small-cell carcinoma, and 14.8 for other types of lung cancer.

Multivariate-adjusted relative and excess risk differed only slightly from age-adjusted relative and excess risk, suggesting that risk factors other than age and smoking habit contribute little to the risk of lung cancer in men.

Discussion

In this large prospective cohort study comparing the relative and excess risk of cigarette smoking on the three major histologic types of lung cancer in Korean men, the relative risk was highest for small-cell carcinoma, whereas the excess risk was highest for adenocarcinoma and squamous cell carcinoma. Our results confirmed that the lower relative risk for adenocarcinoma reflected a higher baseline risk in never smokers for adenocarcinoma compared with small-cell or squamous cell carcinomas.
Our findings, like those of previous studies, showed that the relative risks for all types of lung cancer were significantly higher in current smokers than in never smokers. The relative risks we found, however, were lower than those reported in America and Europe (2, 15-17, 21), but consistent with those reported in Japan and China (3, 14, 18-20). Explanations proposed for our lower relative risks include fewer long-term heavy smokers, the smoking of cigarettes with lower amounts of tar and nicotine (28, 29), later age of initiation, genetic differences such as CYP2A6 polymorphisms (3, 30), and dietary and other nutritional factors.

It is interesting to see that in the present study, the age-adjusted incidence of lung cancer per 100,000 person-years in never smokers (4.5) was higher than that reported in the American Cancer Society Cancer Prevention Study II (5.0; ref. 31) and a Swedish study (3.7; ref. 4). The higher age-adjusted incidence of lung cancer in Korean never smokers may account for the lower relative risk in Koreans compared with Americans and Europeans (2, 15-17, 21).

Our finding that the relative risk of adenocarcinoma was much lower than the risk of squamous and small-cell carcinoma is widely accepted, but our finding in current smokers that squamous cell carcinoma had the highest excess risk at all levels of exposure but adenocarcinoma had a higher excess risk than small-cell carcinoma at 20 pack-years or over is new. It indicates that cigarette smoking is an important risk factor for adenocarcinoma in Korean men. Recently, the Iowa Women’s Health Study, which estimated the age-adjusted incidence rate, relative risk, excess risk, and population attributable risk of smoking, also showed that, in postmenopausal women, adenocarcinoma of the lung is more strongly associated with tobacco smoke exposure than previously recognized (32). Although the incidence rate and excess risk were higher for adenocarcinomas than for small-cell carcinoma in current smokers, adenocarcinoma had the lowest relative risk because of its high baseline incidence rate among never smokers.

In all smoker categories in our study, the age-adjusted incidence rate was higher for adenocarcinomas than for small-cell and squamous cell carcinomas. Additionally, in never smokers, the age-specific incidence rates for adenocarcinoma increased substantially with increasing age, whereas the age-specific incidence rate for squamous cell carcinoma and small-cell carcinoma remained relatively stable (Fig. 1). We also analyzed the incidence rate of lung cancer in subjects ≥50 years old and found it to be very high (data not shown). However, our intent was to show differences of age-specific incidence rate of histologic subtypes by smoking status using incidence in 40- to 49-year-old patients as baseline.

Lung cancer is rare in the large, nonsmoking population (3, 4, 19, 21), but is important in the measurement of risk (4, 19). We found no previous study that evaluated age-adjusted incidence rate according to histologic type in men who never smoked. Only four prospective cohort studies evaluated the association between tobacco smoking and histologic type of lung cancer, and they included a small number of lung cancers among male never-smokers. Specifically, the U.S. Cancer Prevention Study I had five cases of adenocarcinoma and one of squamous cell carcinoma among never-smoking men; Cancer Prevention Study II had six cases of adenocarcinoma and five cases of squamous cell and small-cell carcinoma (21). The Danish population study had only four cases of adenocarcinoma and none of small-cell or squamous cell carcinoma among never-smoking men (19). The recent Japanese Public Health Center study had 15 cases of adenocarcinoma and only 4 cases of small-cell carcinoma and squamous cell carcinoma among never-smoking men (3). Although our population-based approach provided enough

### Table 3. Incidence rate, relative risk, and excess risk of specific types of lung cancer

<table>
<thead>
<tr>
<th>Risk measure</th>
<th>Never (95% CI)</th>
<th>Former (95% CI)</th>
<th>Current (95% CI)</th>
<th>Pack-years of current smokers (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>1.0 (Reference)</td>
<td>3.3 (1.9-5.8)</td>
<td>11.9 (7.2-19.7)</td>
<td>4.9 (2.6-9.3) 8.2 (4.6-14.5) 11.3 (6.7-19.1) 17.2 (10.3-28.7)</td>
</tr>
<tr>
<td>Multivariate</td>
<td>1.0 (Reference)</td>
<td>3.4 (2.0-5.9)</td>
<td>11.7 (7.1-19.4)</td>
<td>5.1 (2.7-9.6) 8.3 (4.6-14.7) 11.3 (6.7-19.3) 16.7 (10.0-27.9)</td>
</tr>
</tbody>
</table>

- *Age-adjusted incidence per 100,000 person-years, adjusting for age or for all covariates (same as in case of relative risk); standard Poisson regression analysis.
- Relative risk modeled using standard Poisson regression analysis adjusted for age and/or all covariates.
- Excess risk per 100,000 person-years, adjusting for age of or for all covariates (same as in case of relative risk); standard Poisson regression analysis.
lung cancer cases (n = 89) in never-smoking men to evaluate the association between cigarette smoking history and type of lung cancer, it had several limitations. First, we did not apply the strict definition of never smokers used by Cancer Prevention Study II (31). Misclassification of never smokers as current smokers would result in an underestimation of lung cancer risk. Second, the study population differed from the general Korean population in socioeconomic and educational status. Because they were government employees and teachers, they may have had behaviors that were conducive to better health. Such an effect was probably small, however, because multivariate analysis, compared with age-adjusted analysis, revealed only minor decreases in risk estimates. Third, enrollment of patients with smoking-related chronic disease might commonly cause misclassification bias. However, we used only incident lung cancer cases not the death rate data. Because the cases were counted based on time of diagnosis of cancer, enrollment of patients with smoking-related chronic disease would not cause the misclassification bias that use of mortality data as outcome causes. Additionally, when we excluded subjects with smoking-related chronic disease and reanalyzed the data, the results did not change significantly. Fourth, a model that contains terms for both age and pack-years may result in overadjustment. When we analyzed the data based on smoking amount adjusted for age and other covariates, there were some changes in incidence rates, relative risks, and excess risks. There were no changes, however, in orders and trends of incidence rates, relative risks, and excess risks among histologic types of lung cancer. Because age is a major risk factor for lung cancer, we could not exclude age in the multivariate model. We focused on comparison of incidence rates, relative risks, and excess risks among histologic types of lung cancer according to pack-years. Finally, we did not adjust for the effects of environmental tobacco smoke and changes in smoking behavior during follow-up. Nevertheless, we believe that the results of our study—that adenocarcinoma of the lung is smoking related and cigarette smoking in Korean men is as important a risk factor for adenocarcinoma as it is for squamous cell or small-cell lung cancer—is important.

References
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