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Cigarette smoking and the subsequent risk of lung carcinoma in the men and women of a large prospective cohort study

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Summary

Background—Whether women are more susceptible than men to lung cancer caused by cigarette smoking has been controversial. We aimed to determine the susceptibility of men and women to cigarette smoking by comparing lung carcinoma incidence rates by stratum of smoking use in the men and women of the National Institutes of Health–AARP cohort.

Methods—The analysis included 279,214 men and 184,623 women from eight U.S. states aged 50 to 71 years at study baseline who were mailed a questionnaire between October 13, 1995 and May 6, 1996 and were followed until December 31, 2003. We present age-standardized incidence rates and multivariate adjusted hazard ratios (HR) adjusted for potential confounders, each with 95% confidence intervals (CI).

Findings—During follow-up, lung carcinomas occurred in 4,097 men and 2,237 women. Incidence rates were 20.3 per 100,000 person-years (95% CI: 16.3–24.3) in never smoking men (99 carcinomas) and 25.3, 95% CI: 21.3–29.3 in never smoking women (152 carcinomas); for this group, the HR for lung carcinoma was 1.3 (95% CI: 1.0–1.8) for women relative to men. Smoking was associated with increased lung carcinoma risk in both men and women. The incidence rate of current smokers of >2 packs per day was 1,259.2 (95% CI: 1,035.0–1,483.3) in men and 1,308.9 (95% CI: 924.2–1,693.6) in women. Among current smokers, in a model adjusted for typical smoking dose, the HR was 0.9 (95% CI: 0.8–0.9) for women relative to men. For former smokers, in a model adjusted for years of cessation and typical smoking dose, the HR was 0.9 (95% CI: 0.9–1.0) for women relative to men.

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Contributors

All authors contributed to the designing of the study, the interpretation of the data, the drafting of the manuscript, and approved the final version of the report. AS obtained funding for the study, ML, AH, and AS acquired the data, and ND, ML, and CA analyzed the data.

Conflicts of interest

The authors declare no conflicts of interest.

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Incidence rates of adenocarcinoma, small cell, and undifferentiated tumors were similar in men and women; incidence rates of squamous tumors in men were twice that in women.

Interpretation—Our study suggests that women are not more susceptible than men to the carcinogenic effects of cigarette smoking in the lung. Future studies should confirm whether incidence rates are indeed higher in never smoking women than in never smoking men.

Introduction

Lung cancer is the leading cause of cancer related mortality worldwide, with almost 1.2 million deaths per year¹ and an estimated 162,000 deaths per year in United States.²

Cigarette smoking is estimated to cause 85–90% of lung cancers in the United States.^{3,4} Worldwide, lung cancer incidence and mortality is three times higher in men than in women.¹ In the United States, there are estimated to be 114,690 incident lung cancers (90,810 deaths) in men and 100,330 incident lung cancers (71,030 deaths) in women in 2008.² Whether men and women have different susceptibilities to the carcinogens in cigarette smoke with respect to lung cancer remains the focus of considerable controversy, with authors debating the merits of using absolute risks (incidence or mortality rates in smokers) or relative risks due to smoking to make this comparison.^{5–9} Few studies have presented both absolute risks and relative risks. Some, but not all, case-control and cohort studies have suggested that smoking causes a significantly larger relative increase in lung cancer risk in women than in men.^{8,10–13} Whereas, results from cohort studies generally find similar incidence and mortality rates in men and women with comparable smoking histories.^{5,14}

Typically, incidence rates of lung cancer in never smoking men and women serve as the denominator for relative risk calculations. Though lung cancer in never smokers is responsible for an estimated 15,000 deaths per year in the United States,³ most epidemiologic studies have limited case numbers in this important group. A recent report analyzed incidence data from 6 large cohort studies.¹⁵ These data suggest higher incidence rates in never smoking women (five studies) than never smoking men (four studies).^{14,15} But, the largest study of men had less than 50 cancers and only three studies included both men and women.^{14,15} These incidence rates are in contrast to those published for mortality, where rates for never smoking men were significantly higher than for never smoking women in most studies⁹ including two very large American Cancer Society cohorts³ with 621 cancers in never smoking men and 1582 cancers in never smoking women.

To address this controversy, we took advantage of the large size of the National Institutes of Health (NIH)-AARP cohort to compare absolute and relative risks of smoking and lung carcinoma in men and women. We present age-standardized incidence rates of lung carcinoma by categories of cigarette use and use multivariate Cox proportional hazard models that estimate the relative increase in lung carcinoma risk due to cigarette smoking. Furthermore, we directly estimate the hazard ratio of lung carcinoma in women compared with men within strata of cigarette use.

Methods

The NIH-AARP Diet and Health study is a large prospective cohort designed to study the association of diet and environmental risk factors and cancer risk. It has been described previously.¹⁶ Between October 13, 1995 and May 6, 1996, a risk factor questionnaire was mailed to 3.5 million members of AARP aged 50–71 years who resided in eight US states (California, Florida, Georgia, Louisiana, Michigan, New Jersey, North Carolina, and Pennsylvania). AARP was formerly known as the American Association of Retired Persons and is a US organization whose membership is open to those at least 50 years of age. Of the

617,119 persons (17.6% of 3.5 million) who returned the questionnaire, 566,402 respondents filled out the survey in satisfactory detail and consented to be in the study. We excluded subjects with cancer or death at baseline (51,217), proxy respondents (15,760), those with total energy intake more than twice the interquartile range (4,419), and those with incomplete information about cigarette use (18,806), or cigar and pipe use (12,363). The resulting cohort included 463,837 participants: 279,214 men and 184,623 women. The conduct of the NIH-AARP Diet and Health Study was reviewed and approved by the Special Studies Institutional Review Board of the U.S. National Cancer Institute (NCI).

Cohort follow-up

As described previously,¹⁷ addresses for members of the NIH-AARP cohort were updated annually by matching the cohort database to that of the National Change of Address database maintained by the U.S. Postal Service, specific changes of address requests from participants, updated addresses returned during yearly mailings, and the Maximum Change of Address database (Anchor Computer). We ascertained vital status by annual linkage of the cohort to the Social Security Administration Death Master File, cancer registry linkage, questionnaire responses, and responses to other mailings.

Identification of lung carcinomas

Incident cancers were identified by linkage between the NIH-AARP cohort membership and 11 state cancer registry databases (8 states from baseline together with Arizona, Nevada, and Texas). We estimate that approximately 90% of cancers will be detected in the cohort by this approach.¹⁷ Cancer sites were identified by anatomic site and histologic code of the International Classification of Disease for Oncology.¹⁸ All primary incident cancers of the bronchus and lung (ICD 34.0 – ICD 34.9) were considered for the present analysis. By histologic code, lung carcinomas included small cell (8002, 8041, 8042, 8044, and 8045), adenocarcinoma (bronchoalveolar: 8250 and 8251 and other: 8140, 8200, 8231, 8260, 8290, 8310, 8323, 8430, 8480, 8481, 8490, and 8550), squamous (8050, 8070, 8071, 8072, 8073, and 8074), undifferentiated/large cell (8012, 8020, 8021, 8022, 8031, and 8032), and other or not otherwise specified carcinoma (8010, 8011, 8046, 8123, 8560, and 8562).

Exposure Assessment

The baseline questionnaire asked about demographics, alcohol intake, tobacco smoking, physical activity, and included a food frequency questionnaire of 124 items. Questionnaires for smoking have shown high reproducibility ($r=0.94$) and validity ($r=0.92$ for women and $r=0.90$ for men relative to serum cotinine levels).^{19,20} Participants were asked if they had smoked more than 100 cigarettes during their life (ever cigarette smokers), smoking intensity (cigarettes smoked per day), whether they were currently smoking, and years since smoking cessation for former smokers. Those who reported quitting within the past year were considered current smokers. To maintain adequate numbers in each stratum for analyses stratified by histologic type, we used a summary variable for cigarette smoking use (never smokers, former smokers of ≤ 1 pack per day, former smokers > 1 pack per day, current smokers of ≤ 1 pack per day, and current smokers > 1 pack per day). Participants were also asked if they had ever smoked pipes or cigars regularly for a year or longer.

Typical alcohol, fruit, vegetable, red meat, processed meat, and total energy intake were calculated from the questionnaire, taking account of frequency and serving size and including individual and mixed foods as described previously.^{21–23}

Statistical Methods

Analyses were performed with SAS version 9.1. A significance level of less than 0.05 was used and all tests were two-sided.

Follow-up time from the date the questionnaire was returned (beginning October 25, 1995) to diagnosis of lung cancer, date of death, or end of follow-up (December 31, 2003), or the date moved out of registry ascertainment area was used as the underlying time metric. Age-standardized incidence rates and 95% confidence intervals were calculated with five year age bands and sex-specific rates standardized to the entire NIH-AARP Diet and Health study population.

Hazard ratios (HR) and 95% confidence intervals (CI) were calculated using Cox proportional hazards regression. Except where noted, all models were adjusted for categorical variables of alcohol intake and education tabulated in Table 1, BMI in kg/m² (<18.5, 18.5–<25, 25–<30, 30–35, and ≥35), usual physical activity throughout the day (sit all day, sit much of the day, stand/walk often/no lifting, lift/carry light loads, and carry heavy loads), vigorous physical activity (never, rarely, 1–3 times/month, 1–2 times/week, 3–4 times/week, 5 or more times per week), and continuous measures for age at cohort entry and intakes of fruit, red meat, processed meat, vegetables, and total energy. For the less than 3% of the cohort that was missing data for a particular covariate, a separate indicator variable for missing was included in the models.

We tested the proportional hazards assumption by modeling interaction terms of time and cigarette use and found no statistically significant deviations. Using age as the underlying time metric did not alter results. Ending follow-up time at the first cancer diagnosis (regardless of site) reduced case numbers slightly, but did not appreciably affect the results. We excluded the first two years of follow-up and the results did not change and are not reported.

Assuming a causal relation between cigarette smoking and lung carcinoma, we calculated multivariate adjusted population attributable risk percents using the delta method as implemented by Spiegelman et al.²⁴

Results

Men and women had similar ages, whereas women had lower daily energy (kcal) intake, higher intake of fruit and vegetables per 1000 kcal/day, less formal education, drank less alcohol, and were less likely to ever smoke cigarettes, pipes, or cigars than men. In contrast, a higher percentage of women 31,542 (17.1% of 184,623) were current smokers than were men 35,256 (12.6% of 279,214) (Table 1). Between October 25, 1995 and December 31, 2003, during 3,334,956 years of follow-up, 6,334 study participants were diagnosed with lung carcinoma (4,097 men and 2,237 women).

In never smokers of cigarettes, the age-standardized incidence rates (per 100,000 person-years) for lung carcinoma were 22.8 (95% confidence interval (CI): 19.0–26.7) for men and 25.4 (95% CI: 21.4–29.5) for women (data not in tables). But, after excluding ever smokers of pipes or cigars from this category, the age-standardized incidence rates became 20.3 (95%CI: 16.3–24.3) for men and 25.3 (95%CI: 21.3–29.3) for women (Table 2). From an age adjusted Cox proportional hazards model, women who did not smoke cigarettes, pipes, or cigars had a HR of 1.2 (95% CI: 1.0–1.6) relative to men in this group (data not in tables). After multivariate adjustment for potential confounders, the risk estimate became 1.3 (95%CI: 1.0–1.8).

Table 2 presents incidence rates for lung carcinoma in cigarette smokers, tabulated by years of cessation and typical dose, along with multivariate adjusted hazard ratios directly comparing lung carcinoma risk in women with that for men of the same smoking stratum. Age-adjusted

hazard ratios were similar to those with multivariate adjustment (data not shown). Current smokers of >40 cigarettes (>2 packs per day), had incidence rates of 1,259.2 (95% CI: 1,035.0–1,483.3, 139 carcinomas) in men and 1,308.9 (95% CI: 924.2–1,693.6, 48 carcinomas) in women. Among this group, women had a HR of 1.1 (95% CI: 0.8–1.6) relative to men. Incidence rates were higher in male current smokers of less than 2 packs of cigarettes per day than in female smokers in the same smoking stratum. As an example, women (535 carcinomas) who reported currently smoking 11–20 cigarettes per day had a HR of 0.8 (95% CI: 0.7–0.9) relative to men (605 carcinomas) in this same smoking stratum. For current smokers overall, incidence rates standardized by age and typical smoking dose were 667.4 (95% CI: 635.0–699.9) in men and 584.8 (95% CI: 550.9–618.7) in women (data not in table). After adjusting for typical smoking dose, the HR for currently smoking women relative to currently smoking men was 0.9 (95% CI: 0.8–0.9; data not in table).

For former smokers compared within stratum of time since quitting and usual dose while smoking, men tended to have higher incidence rates than women, but these differences were not statistically significant. As an example, women that reported smoking >40 cigarettes (>2 packs per day) but stopped smoking more than 10 years ago (51 carcinomas) had a RR of 0.8 (0.6–1.1) relative to men (337 carcinomas) in this group. For former smokers overall, incidence rates standardized by age, years of cessation, and typical smoking dose were 191.7 (95% CI: 183.7–199.7) in men and 185.6 (95% CI: 172.2–198.9) in women (data not in table). From the corresponding Cox proportional hazards model, women had a HR for lung carcinoma of 0.9 (95% CI: 0.9–1.0) relative to men (data not in table).

We also calculated incidence rates standardized by age and all strata of cigarette use along with pipe or cigar use. After standardization by age and smoking use, incidence rates were 196.3 (95% CI: 190.1–202.5) in men and 190.6 (95% CI: 172.2–209.0) in women. In the corresponding Cox proportional hazards model, women had a HR of 0.9 (95% CI: 0.8–0.9) relative to men for lung carcinoma. We estimate that ever smoking cigarettes, pipes, or cigars accounted for 87% (95% CI, 85–89) of lung carcinoma in men and 85% (95% CI, 82–87) of lung carcinoma in women in this cohort.

Among lung carcinomas with known histologic sub-type (5,126 of 6,334 carcinomas), adenocarcinomas were the most frequent sub-type in never smokers (165 of 206, 80%), ever-smokers (2,562 of 4,920, 52%), men (1,574 of 3,321, 47%), and women (988 of 1,805, 55%). (Table 3) The hazard ratios associated with smoking varied by histologic type. For example, relative to never smokers, we found higher hazard ratios associated with currently smoking >1 pack per day for squamous tumors (men: 128.2, 95% CI: 60.1–273.6, 219 carcinomas; women: 139.8, 95% CI: 56.0–349.1, 70 carcinomas) then for adenocarcinomas (men: 17.6 (95% CI: 13.2–23.5, 238 carcinomas; women: 16.4, 95% CI: 12.7–21.1). For adenocarcinomas, never smoking women had borderline increased risk relative to never smoking men (HR for sex, 1.4, 95% CI: 1.0–2.0). The age-standardized incidence rate of adenocarcinoma in never smokers was 12.8 (95% CI: 9.6–16.0) in men and 17.0 (95% CI: 13.7–20.3) in women; among smokers, incidence rates were similar in men and women.

We found no significant differences between men and women by cigarette smoking history for undifferentiated and small cell carcinomas. Incidence rates for squamous tumors were twice as high in men as in women for each stratum of cigarette use.

Discussion

In this large prospective study, we found slightly higher age-standardized incidence rates of lung carcinoma in never smoking women than in never smoking men. But, among ever smokers of comparable amounts of cigarettes, we observed slightly lower incidence rates in women

relative to men. Adenocarcinomas were the most common histological type in both sexes. Among never smokers, incidence rates of adenocarcinoma were higher in women than men, but similar for small cell, squamous, and undifferentiated tumors. In smokers, incidence rates for squamous tumors were twice as high in men as in women, but did not differ for adenocarcinomas, small cell, or undifferentiated tumors.

In this cohort of participants aged 50–79 years, incidence rates per 100,000 person-years for lung carcinoma in never smokers were 20.3 (95% CI: 16.3–24.3; 99 carcinomas) in men and 25.3 (95% CI: 21.3–29.3; 152 carcinomas) in women. Incidence rates of lung cancer per 100,000 person-years in never smokers aged 40–79 years were recently published from six cohorts.¹⁵ The incidence rates for women (data from 5 cohorts) were 14.4 (95% CI: 8.2–23.6; 37 cancers) in the Swedish Uppsala/Orebro Lung Cancer Register cohort (U/OLCR), 15.2 (95% CI: 9.1–24.5; 168 cancers) in the Nurses Health Study, 19.3 (95% CI: 14.2–27.5; 15 cancers) in the First National Health & Nutrition Examination Survey Epidemiologic Follow-Up study (NHEFS), 20.7 (95% CI: 13.5–31.1; 142 cancers) in the Multiethnic cohort (MEC), and 20.8 (95% CI: 13.5–31.2; 91 cancers) in the California Teachers Study (CTS). Rates in men (four cohorts) were 4.8 (95% CI: 2.2–10.6; 10 cancers) in the U/OLCR, 11.2 (95% CI: 6.5–19.0; 43 cancers) in the Health Professionals Follow-Up study, 12.7 (95% CI: 10.2–18.2; 4 cancers) in the NHEFS, and 13.7 (95% CI: 9.0–21.5; 47 cancers) in the MEC. Case numbers in those studies were small, particularly for men. Nevertheless, these results together with those of our study suggest that never smoking women may be at significantly increased risk of lung carcinoma relative to never smoking men. In contrast, previous studies have suggested that lung cancer mortality rates are higher in never smoking men than never smoking women.³ Differences in lung cancer survival^{8,25,26} in men and women might explain these differences between studies of incidence and mortality.

Among ever-smokers (6,083 carcinomas), we found similar age-standardized incidence rates in men and women with comparable cigarette smoking histories, though incidence rates tended to be slightly higher in men than women in the same category, especially among current smokers. Data from five incidence and three mortality studies with substantially smaller case numbers (ranging from 141 to 2,948)^{5,14} are consistent with these findings. Some, but not all, previous studies have reported that the relative increase in risk associated with smoking is greater in women than men.^{8,10–13} We found that smoking increased risk by a similar magnitude in both men and women. It is not clear why results have differed between studies, though most previous studies had small numbers of cancers in never smokers. Our study benefited from a large sample size and a large number of cancers, which provided stable estimates of lung carcinoma incidence rates in never smokers and allowed us to explore individual histologic subtypes. Alternatively, the largest difference between men and women has been reported for the squamous and small cell histological types.^{10,13} Changing prevalence of histologic types over time^{27–29} may also explain study heterogeneity.

We observed similar age-standardized incidence rates for adenocarcinoma, small cell, and undifferentiated tumors in men and women. In contrast, the incidence rates for squamous tumors in men were almost twice that in women and this was true for all categories of smoking, including never smoking. Similar results were observed in US SEER data, where the incidence rate of squamous tumors were higher in men than in women, and the incidence rates of adenocarcinomas, small cell, and undifferentiated tumors were more similar between the sexes.^{27–29} Increased numbers of squamous cancers in men could reflect physiological differences, or differences in inhalation depth or cigarette composition including the use of filters, nicotine content, and type of tobacco used.^{30–34} We did not ascertain cigarette brand preference or inhalation depth.

Our comparison of the incidence of smoking and lung cancer by sex is unlikely to be significantly affected by differential recall of smoking practices in men and women, because previous studies comparing self-reported smoking use and biochemical markers for smoking reported comparable accuracy of assessment in male and female US Caucasians^{19,35} who constitute 93% (424,776 of 458,725) of our cohort.

The strengths of this study include the large size of the cohort and 6,334 incident carcinomas which is substantially larger than previously published studies. The large size provided stable estimates for rates of lung carcinoma among never smokers and allowed us to stratify by histologic type. Cancers were ascertained prospectively allowing the determination of both incidence rates by cigarette smoking stratum and the relative risks associated with cigarette use. Men and women received the same questionnaire, allowing direct comparison within the same study population. We also adjusted our estimates for pipe and cigar use.

This study was limited by the lack of information on the age of smoking initiation at baseline, precluding us from calculating smoking duration and pack-years. In a subset of the cohort who returned a follow-up questionnaire in September 2004 (118,557 men and 72,030 women), the median age at smoking initiation was slightly younger in men (17 years, interquartile range: 13–22) than in women (17 years, interquartile range: 17–22). Age at cessation did not vary by age of initiation. This data suggests that within the same stratum of cessation and typical dose, men may have slightly greater cumulative cigarette exposure than women, perhaps contributing to slightly higher incidence rates in former and current smoking men relative to women observed in this study. In addition, we lacked assessment of exposure to environmental tobacco smoke.

Among never smokers, differences in the exposure to environmental tobacco smoke by men and women could lead to different incidence rates in never smoking women and men in this and other studies. Serum cotinine levels, a well validated biochemical marker of tobacco smoke exposure, were slightly higher in men than women among never smokers in the nationally representative US National Health Interview Survey.^{36,37} Therefore, environmental tobacco smoke likely does not explain the higher incidence rates of lung carcinoma in never smoking women than in never smoking men in this study. Furthermore, though environmental tobacco smoke has strong public health significance, the lung cancer risk conferred by ever cigarette smoking in this and other studies is nearly ten times the estimated risk for environmental tobacco smoke.^{38–40} Thus, we predict that differences in environmental tobacco smoke exposure would not meaningfully affect the incidence rates observed in each stratum of cigarette use, nor would they confound our estimates of the association between cigarette use and lung carcinoma risk by sex.

In addition, smoking was assessed at a single time-point. Participants may have changed their smoking use over time, which could affect lung cancer risk. We also lacked data on inhalation depth and cigarette type. Finally, participants in our cohort were more educated, less likely to be current smokers, and more likely to be non-Hispanic White than the US population,¹⁶ which may limit generalizability to other subpopulations.

In summary, we found that among participants who reported never smoking tobacco in any form, women had slightly higher rates of lung carcinoma than men. But, when we compared smokers with similar smoking histories we found that men tended to have slightly higher incidence rates than women. Our study suggests that women are not more susceptible than men to the carcinogenic effects of cigarette smoking in the lung. Vigorous efforts should continue to be directed at eliminating smoking in both sexes.

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Table 1
Characteristics of the NIH-AARP cohort by sex.

Characteristic [*]	Men	Women
Participants, No.	279,214	184,623
Lung carcinomas, No.	4,097	2,237
Age at entry into the cohort (Age; Median, IQR)	62.7 (57.8–66.7)	62.3 (57.5–66.4)
Alcohol intake, No. (%)		
0 drinks/day	57,204 (20.6)	53,571 (29.1)
> 0 – 1 drinks/day	139,299 (50.0)	106,435 (57.9)
> 1 – 3 drinks/day	51,760 (18.6)	18,963 (10.3)
> 3 drinks/day	30,160 (10.8)	5,007 (2.7)
Body Mass Index (Median, IQR)	26.6 (24.4–29.4)	25.7 (22.9–29.5)
Education, No. (%)		
Less than high school	15,938 (5.9)	11,154 (6.2)
12 years (completed high school)	43,336 (15.9)	46,938 (26.2)
Some post-high school training	88,324 (32.4)	65,871 (36.8)
Completed college	60,551 (22.2)	27,325 (15.3)
Completed graduate school	64,255 (23.6)	27,748 (15.5)
Ethnicity, No. (%)		
Non-Hispanic white	259,140 (93.7)	165,636 (90.9)
Non-Hispanic black	7,407 (2.7)	10,215 (5.6)
Hispanic	5,238 (1.9)	3,478 (1.9)
Asian/Pacific Islander/Native American	4,720 (1.7)	2,891 (1.6)
Fruit intake (Servings per 1000 kcal/day; Median, IQR)	1.3 (0.8–2.1)	1.7 (1.0–2.5)
Vegetable intake (Servings per 1000 kcal/day; Median, IQR)	1.9 (1.4–2.5)	2.2 (1.6–3.1)
Total daily energy intake (kcal; Median, IQR)	1,866 (1,434–2,415)	1,458 (1,119–1,888)
Cigarette Smoking Status, No. (%)		
Never	83,577 (29.9)	81,414 (44.1)
Former	160,381 (57.4)	71,667 (38.8)
Current	35,256 (12.6)	31,542 (17.1)
Usual number of cigarettes smoked (current and former), No. (%)		
≤ 1 packs/day	101,388 (51.8)	72,147 (69.9)
> 1 – 2 packs/day	70,778 (36.2)	25,882 (25.1)
> 2 packs/day	23,471 (12.0)	5,180 (5.0)
Years since quitting smoking (Among former smokers), No. (%)		
Stopped 10 or more years	127,767 (79.7)	50,311 (70.2)
Stopped 5–9 years	21,048 (13.1)	13,106 (18.3)
Stopped 1–4 years	11,566 (7.2)	8,250 (11.5)
Smoked pipes or cigars regularly for a year or longer? No. (%)		
No	198,793 (71.2)	183,848 (99.6)
Yes	80,421 (28.8)	775 (0.4)

* Categories may not add up to 463,837 participants because of missing data.

Table 2
Adjusted incidence rates, hazard ratios, and 95% confidence intervals for cigarette use and lung carcinoma by sex.

Smoking Variable	Men				Women				
	Person-years	No.	Age-standardized* incidence rates/10 ⁵ person-years (95% CI)	Multivariate [†] adjusted hazard ratios (95% CI)	Person-years	No.	Age-standardized* incidence rates/10 ⁵ person-years (95% CI)	Multivariate [†] adjusted hazard ratios (95% CI)	Multivariate [‡] adjusted hazard ratio for women relative to men in each smoking category (95% CI)
Overall	1,996,369	4,097	203.7 (197.4–209.9)		1,338,587	2,237	168.7 (161.8–175.7)		
Never smoked cigarettes, pipes, or cigars	498,237	99	20.3 (16.3–24.3)	1.0 (ref)	597,856	152	25.3 (21.3–29.3)	1.00 (ref)	1.3 (1.0–1.8)
Never smoked cigarettes but smoked pipes or cigars	110,149	38	33.2 (22.6–43.7)	1.6 (1.1–2.4)	455	1	235.4 (0–696.8)	9.2 (1.3–66.3)	6.6 (0.8–52.1)
Stopped ≥ 10 years ago									
1–10 cigarettes/day	205,338	88	41.0 (32.4–49.6)	2.0 (1.5–2.7)	161,772	69	42.2 (32.2–52.1)	1.7 (1.3–2.2)	1.1 (0.8–1.7)
11–20 cigarettes/day	289,846	309	97.4 (86.4–108.4)	4.7 (3.7–5.8)	104,244	117	109.1 (89.3–128.9)	4.4 (3.4–5.6)	1.1 (0.9–1.4)
21–30 cigarettes/day	185,612	323	162.5 (144.7–180.3)	7.8 (6.2–9.8)	50,534	91	180.0 (143.0–217.0)	7.2 (5.5–9.3)	1.0 (0.8–1.3)
30–40 cigarettes/day	122,676	262	197.7 (173.6–221.8)	9.4 (7.5–11.9)	28,717	63	219.3 (165.2–273.5)	8.8 (6.5–11.8)	1.1 (0.8–1.6)
> 40 cigarettes/day	115,077	337	272.1 (242.8–301.4)	12.8 (10.2–16.0)	20,980	51	246.6 (178.9–314.3)	9.9 (7.2–13.6)	0.8 (0.6–1.1)
Stopped 5–10 years ago									
1–10 cigarettes/day	16,735	21	129.2 (73.9–184.5)	6.0 (3.7–9.6)	23,266	32	139.7 (91.2–188.1)	5.5 (3.7–8.0)	1.1 (0.6–2.2)
11–20 cigarettes/day	40,631	114	285.1 (232.8–337.5)	13.0 (9.9–17.1)	31,639	78	248.5 (193.3–303.7)	9.7 (7.4–12.7)	0.8 (0.6–1.1)
21–30 cigarettes/day	36,115	136	388.6 (323.2–454.0)	17.7 (13.7–23.0)	19,049	70	378.6 (289.5–467.6)	15.0 (11.3–20.0)	1.0 (0.7–1.4)
30–40 cigarettes/day	29,220	129	459.0 (379.4–538.5)	20.8 (16.0–27.1)	11,639	55	495.6 (363.9–627.3)	19.5 (14.3–26.6)	1.0 (0.7–1.5)
> 40 cigarettes/day	24,978	150	645.6 (541.4–749.8)	29.2 (22.6–37.7)	8,046	29	382.8 (239.6–526.0)	15.8 (10.6–23.5)	0.6 (0.4–1.0)
Stopped 1–<5 years ago									
1–10 cigarettes/day	9,717	20	225.6 (125.4–325.8)	10.6 (6.5–17.1)	14,706	29	218.0 (138.1–298.0)	8.0 (5.4–12.0)	0.8 (0.4–1.6)
11–20 cigarettes/day	23,748	104	451.8 (364.8–538.9)	20.4 (15.5–27.0)	21,417	79	377.5 (294.1–460.9)	14.6 (11.1–19.1)	0.7 (0.5–1.1)
21–30 cigarettes/day	20,519	111	581.5 (472.1–690.9)	25.7 (19.6–33.8)	12,178	54	477.5 (348.7–606.3)	18.4 (13.4–25.1)	0.9 (0.6–1.3)
30–40 cigarettes/day	14,657	93	673.4 (535.0–811.7)	29.5 (22.2–39.2)	6,528	35	553.8 (370.0–737.5)	21.2 (14.7–30.7)	0.8 (0.5–1.2)
> 40 cigarettes/day	11,257	84	828.3 (648.8–1,007.8)	35.8 (26.7–48.1)	3,648	18	516.7 (271.8–761.5)	21.5 (13.2–35.1)	0.7 (0.4–1.1)
Current smokers									
1–10 cigarettes/day	49,323	223	479.3 (416.2–542.5)	20.7 (16.3–26.3)	68,806	235	358.6 (312.4–404.7)	13.4 (10.9–16.5)	0.7 (0.6–0.9)
11–20 cigarettes/day	90,311	605	723.8 (665.6–782.0)	30.5 (24.6–37.9)	94,060	535	612.8 (560.1–665.5)	22.5 (18.8–27.1)	0.8 (0.7–0.9)
21–30 cigarettes/day	57,048	429	867.2 (782.5–951.8)	35.9 (28.7–44.8)	39,611	247	689.4 (601.3–777.6)	25.2 (20.5–31.0)	0.8 (0.7–1.0)
30–40 cigarettes/day	32,622	283	988.1 (867.9–1,108.4)	42.6 (33.8–53.8)	15,295	149	1,112.6 (927.2–1,298.0)	40.7 (32.3–51.2)	1.0 (0.8–1.3)
> 40 cigarettes/day	12,553	139	1,259.2 (1,035.0–1,483.3)	54.9 (42.2–71.4)	4,142	48	1,308.9 (924.2–1,693.6)	47.3 (34.0–65.8)	1.1 (0.8–1.6)

Indicates confidence intervals; ref, reference; No., number.

CI indicates confidence intervals; ref, reference; No., number.

* Age-standardized incidence rates calculated by direct standardization to the entire AARP cohort; see methods for details.

[†] Hazard ratios and 95% confidence intervals (CI) from Cox models adjusted for age at entry into cohort, body mass index, education, vigorous physical activity, usual activity throughout the day, alcohol intake, fruit intake, vegetable intake, red meat intake, processed meat intake, pipe or cigar use, and total energy intake. For hazard ratios associated with smoking, age-adjusted and multivariate adjusted estimates were similar.

Adjusted incidence rates, hazard ratios, and 95% confidence intervals for cigarette use and lung carcinoma by sex and histology.

Table 3

Histological type and Smoking Status	Men				Women			
	Person-years	No.	Age-standardized* incidence rates/10 ⁵ person-years (95% CI)	Multivariate [†] adjusted hazard ratios (95% CI)	Person-years	No.	Age-standardized* incidence rates/10 ⁵ person-years (95% CI)	Multivariate [†] adjusted hazard ratios (95% CI)
								Multivariate [†] adjusted haza ratio for women relative to men in each smoking category (95% CI)
Adenocarcinoma Never smoked cigarettes, pipes, or cigars Former cigarette smoker ≤ 1 pack/day Former cigarette smoker > 1 pack/day Current cigarette smoker ≤ 1 pack/day Current cigarette smoker > 1 pack/day	1,996,369 498,237	1574 63	78.3 (74.4–82.2) 12.8 (9.6–16.0)	1.0 (ref)	1,338,587 597,856	988 102	74.4 (69.8–79.0) 17.0 (13.7–20.3)	1.00 (ref) 1.4 (1.0–2.0)
	586,015	301	48.7 (43.2–54.2)	3.9 (3.0–5.1)	357,043	205	56.9 (49.1–64.7)	3.2 (2.5–4.1)
	560,112	686	118.5 (109.6–127.4)	9.2 (7.1–12.0)	161,319	221	140.2 (121.7–158.7)	7.9 (6.2–10.0)
	139,634	268	203.9 (179.3–228.5)	14.0 (10.6–18.5)	162,866	294	188.4 (166.7–210.2)	10.2 (8.1–12.8)
	102,223	238	259.5 (225.1–293.9)	17.6 (13.2–23.5)	59,048	166	302.1 (254.8–349.4)	16.4 (12.7–21.1)
								1.1 (0.9–1.4)
Small Cell Never smoked cigarettes, pipes, or cigars Former cigarette smoker ≤ 1 pack/day Former cigarette smoker > 1 pack/day Current cigarette smoker ≤ 1 pack/day Current cigarette smoker > 1 pack/day	1,996,369 498,237	571 7	28.4 (26.1–30.7) 1.4 (0.4–2.5)	1.00 (ref)	1,338,587 597,856	369 7	27.8 (25.0–30.7) 1.2 (0.3–2.0)	1.00 (ref) 0.6 (0.2–1.9)
	586,015	61	10.1 (7.5–12.6)	6.3 (2.9–13.9)	357,043	38	10.5 (7.2–13.9)	9.2 (4.1–20.7)
	560,112	181	31.1 (26.5–35.6)	18.6 (8.7–39.8)	161,319	59	37.6 (28.0–47.3)	31.7 (14.5–69.6)
	139,634	151	116.4 (97.7–135.1)	65.2 (30.4–139.8)	162,866	153	101.4 (85.2–117.6)	83.4 (39.0–178.6)
	102,223	165	184.4 (155.1–213.6)	98.2 (45.7–210.9)	59,048	112	207.5 (167.9–247.1)	168.4 (77.9–364.3)
								1.2 (0.9–1.6)
Squamous Never smoked cigarettes, pipes, or cigars Former cigarette smoker ≤ 1 pack/day Former cigarette smoker > 1 pack/day Current cigarette smoker ≤ 1 pack/day Current cigarette smoker > 1 pack/day	1,996,369 498,237	921 7	45.8 (42.8–48.7) 1.5 (0.4–2.6)	1.0 (ref)	1,338,587 597,856	317 5	24.0 (21.3–26.6) 0.8 (0.1–1.6)	1.00 (ref) 0.3 (0.1–1.2)
	586,015	131	21.1 (17.4–24.7)	13.0 (6.0–27.8)	357,043	54	15.0 (11.0–19.0)	19.2 (7.7–48.0)
	560,112	359	61.8 (55.4–68.2)	36.0 (17.0–76.3)	161,319	71	45.4 (34.8–56.0)	57.2 (23.0–141.9)
	139,634	200	154.9 (133.3–176.5)	83.1 (39.0–177.1)	162,866	116	76.5 (62.5–90.6)	83.1 (33.8–204.3)
	102,223	219	247.6 (213.6–281.6)	128.2 (60.1–273.6)	59,048	70	138.7 (105.5–171.9)	139.8 (56.0–349.1)
								0.6 (0.4–0.8)
Undifferentiated Never smoked cigarettes, pipes, or cigars Former cigarette smoker ≤ 1 pack/day Former cigarette smoker > 1 pack/day Current cigarette smoker ≤ 1 pack/day	1,996,369 498,237	255 5	12.7 (11.1–14.2) 1.0 (0.1–2.0)	1.0 (ref)	1,338,587 597,856	131 10	9.9 (8.2–11.6) 1.7 (0.6–2.7)	1.00 (ref) 2.1 (0.6–7.1)
	586,015	37	6.0 (4.1–8.0)	6.2 (2.4–15.8)	357,043	22	6.1 (3.5–8.6)	3.8 (1.8–8.0)
	560,112	101	17.4 (14.0–20.8)	17.0 (6.9–42.1)	161,319	30	19.0 (12.2–25.8)	11.5 (5.6–23.6)
	139,634	48	36.7 (26.3–47.2)	31.0 (12.2–78.6)	162,866	51	32.8 (23.7–41.9)	18.4 (9.2–36.7)
								1.1 (0.7–1.8)
								0.8 (0.5–1.5)

Histological type and Smoking Status	Men			Women			Multivariate [†] adjusted hazard ratio for women relative to men in each smoking category (95% CI)		
	Person-years	No.	Age-standardized [*] incidence rates/10 ⁵ person-years (95% CI)	Multivariate [†] adjusted hazard ratios (95% CI)	Person-years	No.		Age-standardized [*] incidence rates/10 ⁵ person-years (95% CI)	Multivariate [†] adjusted hazard ratios (95% CI)
Current cigarette smoker >1 pack/day	102,223	59	67.8 (50.0–85.6)	52.3 (20.7–132.1)	59,048	18	32.7 (17.0–48.5)	18.0 (8.1–39.9)	0.5 (0.3–1.0)

CI indicates confidence intervals; ref, reference; No., number

For each histologic type, lung cancer cancers with different histologies were censored at diagnosis date.

^{*} Age-standardized incidence rates calculated by direct standardization to the entire AARP cohort; see methods for details.

[†] Hazard ratios and 95% confidence intervals (CI) from Cox models adjusted for age at entry into cohort, body mass index, education, vigorous physical activity, usual activity throughout the day, alcohol intake, fruit intake, vegetable intake, red meat intake, processed meat intake, pipe or cigar use, and total energy intake.

For hazard ratios associated with smoking, age-adjusted and multivariate adjusted estimates were similar.