American Journal of Epidemiology
Published by Oxford University Press on behalf of the Johns Hopkins Bloomberg School of Public Health 2013.

Vol. 177, No. 7
DOI: 10.1093/aje/kws445
Advance Access publication:
February 20, 2013

Original Contribution

Are Women Who Smoke at Higher Risk for Lung Cancer Than Men Who Smoke?

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Initially submitted November 29, 2011; accepted for publication May 24, 2012.

Worldwide lung cancer incidence is decreasing or leveling off among men, but rising among women. Sex differences in associations of tobacco carcinogens with lung cancer risk have been hypothesized, but the epidemiologic evidence is conflicting. We tested sex-smoking interaction in association with lung cancer risk within a population-based case-control study, the Environment and Genetics in Lung Cancer Etiology (EAGLE) Study (Lombardy, Italy, 2002–2005). Detailed lifetime smoking histories were collected by personal interview in 2,100 cases with incident lung cancer and 2,120 controls. Odds ratios and 95% confidence intervals for pack-years of cigarette smoking were estimated by logistic regression, adjusted for age, residence area, and time since quitting smoking. To assess sex-smoking interaction, we compared the slopes of odds ratios for logarithm of pack-years in a model for men and women combined. Overall, the slope for pack-years was steeper in men (odds ratio for female-smoking interaction = 0.39, 95% confidence interval: 0.24, 0.62; $P < 0.0001$); after restriction to ever smokers, the difference in slopes was much smaller (odds ratio for interaction = 0.63, 95% confidence interval: 0.29, 1.37; $P = 0.24$). Similar results were found by histological type. Results were unchanged when additional confounders were evaluated (e.g., tobacco type, inhalation depth, Fagerström-assessed nicotine dependence). These findings do not support a higher female susceptibility to tobacco-related lung cancer.

case-control studies; lung cancer; sex differences; smoking

Abbreviations: EAGLE, Environment and Genetics in Lung Cancer Etiology; FTND, Fagerström Test for Nicotine Dependence; SHS, secondhand smoke.

Editor's note: *An invited commentary on this article appears on page 613.*

Lung cancer is the leading cause of cancer mortality worldwide, with almost 1.4 million deaths per year (18% of total cancer mortality) (1). Among men, it is still the most common cancer (1.1 million cases, 16.5% of the total); among women, it is fourth in frequency (513,000 cases, 8.5% of all cancers) but second in the number of deaths (427,000 deaths, 12.8% of the total) (1). Tobacco smoking is the major cause, accounting for 80% of the worldwide lung cancer burden in males and at least 50% in females (1).

In the last 3 decades, lung cancer incidence rates worldwide have decreased or leveled off among men, but have risen among women (1). This increase (by 600% in the last 50 years) has been defined as a "contemporary epidemic" (2). Additionally, women show a different clinical pattern of lung cancer than men: They tend to be younger, to be never smokers, to have the adenocarcinoma histological type, and to have improved survival rates for all stages at diagnosis (2, 3).

Biologically, a number of explanations have been proposed for sex differences in lung cancer susceptibility. Estrogen receptors are present in both normal and neoplastic lung tissues and could accelerate the metabolism of smoke-related carcinogens in a dose-dependent way, as suggested by higher levels of polycyclic aromatic hydrocarbons–DNA adducts in female smokers compared with males (4). Inherited genetic polymorphisms affecting activating and detoxifying enzymes could explain a different susceptibility

between the sexes to tobacco carcinogens (5). In addition, several lifestyle and behavioral factors related to smoking habits or environmental and occupational exposures could account for some sex differences (3, 6).

Epidemiologic studies are conflicting. Several case-control studies (7–10), but not all (11–13), have found a higher relative risk among women compared with men for the same level of smoking exposure. On the contrary, the majority of cohort studies (14–23), with a few exceptions (24, 25), and a recent meta-analysis including a Japanese cohort and case-control studies (26) found no difference between the sexes or even a higher rate ratio in men. The issue is vigorously debated because of the potential impact on health policy (24). Debate still exists about the best study design (cohort vs. case-control), risk estimate measure (absolute vs. relative), model of interaction (additive vs. multiplicative), treatment of never smokers (inclusion vs. exclusion), and potential confounders (e.g., depth of inhalation, tobacco type) with which to answer this question (27–31).

To address these issues, we took advantage of data from the Environment And Genetics in Lung cancer Etiology (EAGLE) Study, a large population-based case-control study conducted in the Lombardy region of Italy between 2002 and 2005. The EAGLE Study, which was designed to explore the role of tobacco smoking in lung cancer risk in combination with other genetic and environmental factors (32), allowed us to exploit very detailed lifetime smoking histories collected by personal interview with the index subjects.

Our aim was to evaluate the interaction between female sex and tobacco smoking in association with lung cancer risk using different exposure-response models and taking into account several potential confounders and effect modifiers. Moreover, the large sample size allowed us to perform analyses according to the main histological types of lung cancer.

MATERIALS AND METHODS

Study design

The EAGLE Study (32) included 2,100 incident lung cancer cases (448 women and 1,652 men) and 2,120 population controls (500 women and 1,620 men). The subjects were enrolled in April 2002–June 2005 in 216 municipalities (including the cities of Milan, Monza, Brescia, Pavia, and Varese) in Lombardy, the most developed and populated (over 9 million inhabitants) region of Italy. Subjects were 35–79 years of age at diagnosis (cases) or at sampling/enrollment (controls). Response rates (participants/eligible subjects) were 86.6% (cases) and 72.4% (controls).

Cases were persons with newly diagnosed primary cancer of the trachea, bronchus, or lung, of any stage and morphology, verified by means of tissue pathology (67.0%), cytology (28.0%), or review of clinical records (5.0%). They were recruited in 13 hospitals which cover over 80% of the lung cancer cases from the study area. Controls were randomly sampled from population databases of the area, frequency-matched to cases by residence (5 areas), sex, and age (5-year categories), and contacted through family physicians. The study was approved by local and US National Cancer Institute institutional review boards, and all participants signed an informed consent form.

Data collection

All subjects underwent a computer-assisted personal interview for collection of extensive information on the major risk factors for lung cancer and completed a self-administered questionnaire on aspects of behavior possibly associated with smoking persistence. In particular, information on lifetime tobacco smoking was collected, including numbers of cigarettes, cigars, pipes, and cigarillos smoked per day; age at initiation/quitting; number of quitting attempts and time between attempts; inhalation pattern; percentage of each cigarette smoked; and secondhand smoke (SHS) exposure during childhood, at the workplace, and at home during adulthood. The 6-item Fagerström Test for Nicotine Dependence (FTND) was administered to assess nicotine dependence (33).

Statistical analysis

We calculated odds ratios and 95% confidence intervals for cigarette smoking exposure, separately for males and females, in unconditional multiple logistic regression models, adjusted for residential area (5 categories, including the 5 cities and their surrounding municipalities), age (5-year categories) and time since quitting smoking (categorical: 0 for never/current smokers; otherwise, 0.5–0.9, 1–1.9, 2–4.9, 5–9.9, 10–19.9, 20–29.9, or ≥30 years). We defined as never smokers subjects who had smoked fewer than 100 cigarettes in their lifetime.

The main exposure-response models assessed cumulative cigarette exposure (pack-years) treated as either a categorical (0 for never smokers; otherwise, 1–19, 20–39, or ≥40 pack-years) or a continuous ($\log_{10}$ (1 + pack-years/5)) variable (9). We first fitted models separately for men and women. However, although they are useful for showing exposure-response patterns within sexes, the odds ratios from separate models cannot be safely compared between the sexes because they are obtained using different intercepts (reference categories). Therefore, to formally assess interaction (on the multiplicative scale), we fitted models for men and women combined including sex-smoking product terms. We evaluated the latter using the likelihood ratio test for models containing categorical pack-years, and Wald-based 95% confidence intervals and tests when fitting models estimating the odds ratio-smoking slope using continuous pack-years. We used the male sex as the reference group, so a positive or negative interaction corresponds to higher or lower odds ratios in women, respectively.

We used the "floating trend" approach to visualize the relationship between adjusted odds and pack-year categories in the two sexes. In the floating trend approach, the lack of dependence of point and confidence interval estimates in different exposure categories on the reference category provides a reference-free representation of the dose-response relationship (34); this is especially advantageous in our study for men, because almost all male cases were smokers.

Table 1. Selected Characteristics of Lung Cancer Cases and Controls With Interview Data Available, by Sex, the EAGLE Study, Lombardy, Italy, 2002–2005[a,b]

	Women						Men					
	Cases			Controls			Cases			Controls		
	No.[c]	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)
Enrolled	448			500			1,652			1,620		
Interviewed	406	90.6		499	99.8		1,537	93.0		1,617	99.8	
Area of residence												
Milan	288	70.9		349	69.9		987	64.2		1,089	67.3	
Monza	24	5.9		23	4.6		109	7.1		94	5.8	
Brescia	47	11.6		53	10.6		203	13.2		194	12.0	
Pavia	21	5.2		37	7.4		107	7.0		92	5.7	
Varese	26	6.4		37	7.4		131	8.5		148	9.2	
P value			0.55						0.17			
Age, years			64.8 (10.1)			64.1 (10.1)			66.8 (7.9)			65.8 (8.1)
P value			0.32						< 0.001			
Educational level												
None	21	5.2		24	4.8		91	5.9		66	4.1	
Elementary school	128	31.5		143	28.7		625	40.7		431	26.7	
Middle school	134	33.0		158	31.7		424	27.6		455	28.1	
High school	104	25.6		135	27.1		314	20.4		441	27.3	
University	19	4.7		39	7.8		83	5.4		224	13.9	
P value			0.35						< 0.001			
Employed in an occupation associated with lung cancer												
Never	379	93.3		471	94.4		1,015	66.0		1,171	72.4	
List B (exposure to suspected carcinogens)	24	5.9		26	5.2		345	22.5		346	21.4	
List A (exposure to known carcinogens)	3	0.7		2	0.4		177	11.5		100	6.2	
P value			0.71						<0.001			
Other cancer(s)[d]												
No	336	82.8		448	89.8		1,306	85.0		1,473	91.1	
Yes	70	17.2		51	10.2		231	15.0		144	8.9	
P value			0.002						<0.001			
Lung cancer morphology (histological type)												
Adenocarcinoma	220	54.2					582	37.9				
Squamous-cell carcinoma	45	11.1					459	29.9				
Large-cell carcinoma	28	6.9					61	4.0				
Non-small-cell carcinoma NOS	34	8.4					142	9.2				
Small-cell carcinoma	38	9.4					157	10.2				
Other	26	6.4					65	4.2				
Data not available	15	3.7					71	4.6				
P value						<0.001						

Abbreviations: EAGLE, Environment and Genetics in Lung Cancer Etiology; NOS, not otherwise specified; SD, standard deviation.

[a] *P* values were calculated from the χ^2 test (categorical variables) or Student's *t* test (continuous variables) for comparison between cases and controls of the same sex or between cases of different sexes (for lung cancer morphology only).

[b] Percentages may not add to 100.0 because of rounding.

[c] Number of participants.

[d] Primary cancer(s) (previously or newly diagnosed) other than lung cancer.

Table 2. Smoking Habits of Lung Cancer Cases and Controls, by Sex, the EAGLE Study, Lombardy, Italy, 2002–2005[a,b]

	Women						Men					
	Cases			Controls			Cases			Controls		
	No.[c]	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)
No. interviewed	406			499			1,537			1,617		
Cigarette smoking status												
Never smoker	103	25.4		282	56.5		29	1.9		397	24.6	
Former smoker (quit >6 months previously)	116	28.6		110	22.0		723	47.0		799	49.4	
Current smoker	187	46.1		107	21.4		785	51.1		420	26.0	
Unknown	0	0.0		0	0.0		0	0.0		1	0.1	
P for cases vs. controls			<0.001						<0.001			
P for women vs. men	<0.001				<0.001							
Pack-years of smoking[d]			32.6 (21.1)			16.4 (16.4)			51.8 (28.1)			29.3 (22.4)
P for cases vs. controls			<0.001						<0.001			
P for women vs. men	<0.001				<0.001							
Duration of smoking, years[d]			38.5 (12.6)			28.1 (15.2)			44.0 (11.3)			32.7 (14.9)
P for cases vs. controls			<0.001						<0.001			
P for women vs. men	<0.001				<0.001							
Intensity of smoking, packs/day[d]			0. 8 (0.4)			0.5 (0.4)			1.2 (0.6)			0.8 (0.5)
P for cases vs. controls			<0.001						<0.001			
P for women vs. men	<0.001				<0.001							
Years since quitting smoking[d]			4.2 (8.4)			9.2 (12.8)			5.9 (9.5)			14.1 (14.5)
P for cases vs. controls			<0.001						<0.001			
P for women vs. men	<0.001				<0.001							
Percentage of each cigarette smoked[d]												
25	5	1.7		1	0.5		1	0.1		3	0.2	
50	17	5.6		11	5.1		62	4.1		36	3.0	
75	113	37.3		53	24.4		449	29.8		295	24.2	
100	168	55.4		152	70.0		995	66.0		885	72.6	
Unknown							1	0.1				
P for cases vs. controls			0.006						0.002			
P for women vs. men	<0.001				0.39							

Table continues

Table 2. Continued

	Women						Men					
	Cases			Controls			Cases			Controls		
	No.[c]	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)
Inhalation pattern[d]												
None	21	6.9		36	16.6		24	1.6		75	6.1	
Slight (back to throat)	59	19.5		53	24.4		123	8.2		130	10.7	
Moderate (partly into chest)	91	30.0		92	42.4		389	25.8		479	39.3	
Deep (deeply into chest)	122	40.3		34	15.7		949	62.9		534	43.8	
Unknown	10	3.3		2	0.9		23	1.5		2	0.2	
P for cases vs. controls			<0.001						<0.001			
P for women vs. men	<0.001				<0.001							
FTND score[d]			4.0 (2.4)			1.9 (2.4)			4.8 (2.4)			2.9 (2.6)
P for cases vs. controls			<0.001						<0.001			
P for women vs. men	0.004				<0.001							
Smoking of pipes, cigars, or cigarillos												
Never	401	98.8		497	99.6	1,270	82.6		1,308	80.9		
Ever	5	1.2		2	0.4	267	17.4		309	19.1		
P for cases vs. controls			0.16						0.21			
P for women vs. men	<0.001				<0.001							

Abbreviations: EAGLE, Environment and Genetics in Lung Cancer Etiology; FTND, Fagerström Test for Nicotine Dependence; SD, standard deviation.

[a] *P* values were calculated from the χ^2 test (categorical variables) or Mann-Whitney test (continuous variables) for comparison between cases and controls of the same sex or between cases of different sexes (for lung cancer morphology only).

[b] Percentages may not add to 100.0 because of rounding.

[c] Number of participants.

[d] Ever cigarette smokers only.

The odds represent not incidence odds but simply arbitrary case-control ratios that can be compared to visualize patterns and test for trends (34). We plotted the odds on a logarithmic scale for never/current smokers aged 65–69 years residing in area 1 (Milan), the largest category in our study.

The same analyses were repeated among ever smokers only, by smoking status, and with adjustment for smoking of other types of tobacco (i.e., pipes, cigars, and cigarillos; dichotomous variable: ever/never), inhalation depth (4 categories: none, slight, moderate, or deep), and FTND score (3 categories: score of 0–3, no dependence; 4 or 5, dependence; 6–10, severe dependence). We also explored the role of SHS exposure (any exposure in childhood, or adulthood exposure at home and at work) either as a confounder (by adjusting for SHS exposure) or as an effect modifier (by analyzing sex-smoking interactions separately among those ever and never exposed to SHS exposure). In further analyses, we also adjusted for education as a surrogate for socioeconomic status (4 categories: none, elementary school, middle school, or high school/higher degree) and occupations known or suspected to be associated with lung cancer risk (35) (dichotomous variable: ever/never). Among ever smokers, we also created a surrogate for cumulative cigarette "dose," by multiplying the cumulative cigarette exposure (pack-years) by the reported percentage of each cigarette smoked (25%, 50%, or ≥75%). We used this variable both as a continuous variable ($\log_{10}$ (1 + dose/5)) and as a categorical variable (0 for never smokers; otherwise 1–19, 20–29, or ≥40 pack-years).

Separate analyses were performed for the main lung cancer histological types (adenocarcinoma, squamous-cell carcinoma, and small-cell carcinoma) in a multinomial logistic regression model. We restricted the analyses for squamous- and small-cell carcinomas to ever smokers only, given the extreme paucity of never smokers among cases with these histological types. All *P* values were 2-sided. Analyses were carried out using Stata, version 11 (StataCorp LP, College Station, Texas).

RESULTS

Of the 2,100 cases and 2,120 controls enrolled in our study, 1,943 (92.5%) and 2,116 (99.8%) were interviewed, respectively. In particular, interviews were obtained from 406 women and 1,537 men among cases and 499 women and 1,617 men among controls (Table 1). Two-thirds of the subjects came from the area of Milan (Lombardy's capital). Among men, controls had a higher educational level. Male cases had held more jobs associated with lung cancer risk during their working lives than controls. Approximately 14%–15% of cases and 6%–7% of controls had previously or newly diagnosed primary cancer(s) other than lung cancer. The majority of lung cancers were adenocarcinomas (>50% in women).

Among cases, one-fourth of women were never smokers as compared with only 2% of men; among controls, 57% of women were never smokers as compared with 25% of men (Table 2). In both sexes, current smokers comprised approximately 50% of cases and less than 30% of controls. Almost half of men (cases or controls) were former smokers (i.e., they had quit smoking ≥6 months previously), as compared with less than 30% of women. The cumulative exposure, duration, and average intensity of cigarette smoking were substantially higher in men and, within both sexes, for lung cancer cases. Men and controls had refrained from smoking for a longer period of time but also had more frequently smoked 100% of each cigarette. Inhalation depth was greater among cases and men. Very few women had smoked other types of tobacco, compared with almost 20% of both male cases and male controls. Nicotine dependence, as assessed with the FTND, was higher for men and for cases. The smoking pattern differed (i.e., was more dependent) between cases and controls for all 6 items on the Fagerström test and between men and women for almost all items (see Web Table 1, available at http://aje.oxfordjournals.org/).

Lung cancer odds ratios for pack-years (categorical) were higher in men than in women, with a negative female sex-smoking interaction ($P = 0.0009$) (Table 3). When we restricted analyses to ever smokers, the odds ratios for women were slightly higher than those for men, but there was no evidence of an interaction ($P = 0.55$) (Table 3). The floating trend graph (Figure 1) shows a higher increase in odds from never smokers to the category 1–19 pack-years in men. Conversely, for medium (20–29 pack-years) and high (≥40 pack-years) categories, the lines appear substantially parallel across the two sexes. Similar results were obtained for pack-years as a log-transformed continuous variable: a negative female sex-smoking interaction (odds ratio = 0.39, 95% confidence interval: 0.24, 0.62; $P < 0.0001$) in all subjects and no interaction (odds ratio = 0.63, 95% confidence interval: 0.29, 1.37; $P = 0.24$) among ever smokers (Table 3). We also explored the association within former and current smokers separately and found no major difference (Table 4). Odds ratios were slightly higher in men for the highest category of pack-years in both subgroups and for the continuous variable among current smokers only, but there was no sex-smoking interaction (Table 4).

In the analyses for the main lung cancer histological types, odds ratios for pack-years (categorical) among adenocarcinoma cases were higher in men than in women, with a negative female sex-smoking interaction ($P = 0.005$) (Table 5). In the analyses restricted to former and current smokers, there was no evidence of interaction ($P = 0.76$ and $P = 0.47$, respectively). These results were confirmed using pack-years as a log-transformed continuous variable (Table 5). Similarly, although the findings were based on a smaller number of subjects, no significant sex-smoking interaction was found for squamous- and small-cell carcinoma cases, either treating pack-years as a categorical variable or treating it as continuous (Web Tables 2 and 3).

We performed further analyses, individually adjusting the same logistic regression models for education, having ever worked in an occupation associated with lung cancer, smoking of other tobacco products, inhalation depth, SHS exposure, or FTND score; using cumulative cigarette "dose," as both a continuous and a categorical variable; or exploring subgroups of "low-exposed" subjects (current smokers of fewer than 10 cigarettes/day) and long-term

Table 3. Cumulative Exposure to Cigarette Smoking and Associated Odds Ratios for Lung Cancer Among All Subjects and Ever Smokers, by Sex, the EAGLE Study, Lombardy, Italy, 2002–2005

Exposure Measure	Cigarette Smoking Exposure								Odds of Lung Cancer							
									All Subjects				Ever Smokers			
	Women				Men				Women		Men		Women		Men	
	Cases		Controls		Cases		Controls									
	No.	%	No.	%	No.	%	No.	%	OR[a]	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Categorical variable, pack-years																
Never smoker	103	25.4	282	56.5	29	1.9	397	24.6	1.0	Referent	1.0	Referent				
1–19	87	21.4	147	29.5	118	7.7	464	28.7	1.8	1.1, 2.9	5.9	3.7, 9.5	1.0	Referent	1.0	Referent
20–39	124	30.5	49	9.8	420	27.3	413	25.5	6.9	4.4, 10.7	18.2	12.0, 27.7	4.0	2.5, 6.4	3.1	2.3, 4.0
≥40	92	22.7	21	4.2	967	62.9	341	21.1	12.3	7.2, 21.2	42.2	28.1, 63.4	7.2	3.9, 13.4	7.1	5.4, 9.4
Data not available	0	0	0	0	3	0.2	2	0.1								
$P_{interaction}$[b]										0.0009[c]				0.55		
Continuous variable (log_{10} (1 + pack-years/5))									11.3	7.6, 16.8	28.4	21.2, 38.1	37.5	15.3, 92.0	27.4	18.0, 41.7
Female sex-smoking interaction									0.39	0.24, 0.62			0.63	0.29, 1.37		
$P_{interaction}$[b]										<0.0001[d]				0.24		

Abbreviations: CI, confidence interval; EAGLE, Environment and Genetics in Lung Cancer Etiology; OR, odds ratio.

[a] ORs and 95% CIs from unconditional logistic regression models, adjusted for residential area, age, and years since quitting smoking.

[b] *P* values were calculated from the likelihood ratio test or Wald test for the product of sex and pack-years (pack-years as a categorical or continuous (log_{10} (1 + pack-years/5)) variable, respectively).

[c] Negative female sex-smoking interaction coefficients for all of the pack-year categories evaluated.

[d] Negative female sex-smoking interaction coefficient.

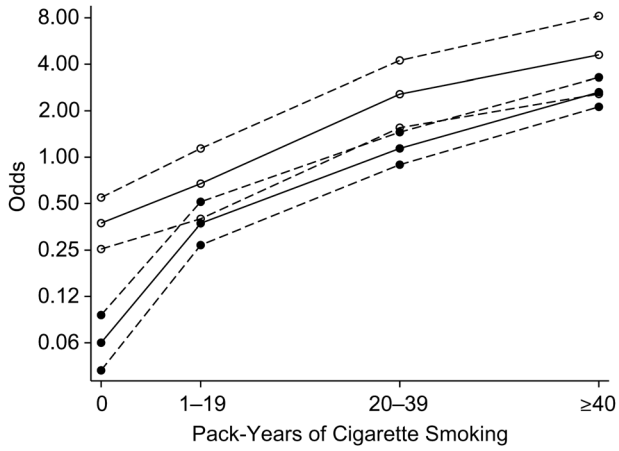

Figure 1. Floating trends in the odds of lung cancer on a logarithmic scale according to pack-years of cigarette smoking, adjusted for residence area, age, and years since quitting smoking, in females (○) and males (●), the EAGLE Study, Lombardy, Italy, 2002–2005. Estimates shown are for never smokers (0 pack-years) and current smokers aged 65–69 years residing in area 1 (Milan). Dashed lines, 95% confidence interval. EAGLE, Environment and Genetics in Lung Cancer Etiology.

quitters (persons who had refrained from smoking for ≥10 years). We also conducted analyses stratified by age or SHS exposure. Results were always virtually unchanged (data not shown).

DISCUSSION

In a large population-based case-control study with detailed information on lifetime smoking habits, direct interviews with cases, and a high response rate in both cases and controls, we found a clear negative interaction between female sex and tobacco smoking when using never smokers as the reference category, corresponding to higher odds ratios in men for a given level of lifetime cumulative smoking exposure (measured in pack-years). In contrast, the analyses restricted to ever smokers, based on the more stable reference of light smokers, showed no significant sex-smoking interaction. This finding was also depicted by the floating trend graph (Figure 1), which showed that the exposure-response curves in men and women were substantially parallel. Even assuming a worst-case scenario for women, the relatively tight confidence interval for sex-smoking interaction in ever smokers (e.g., for pack-years as a continuous variable, 95% CI: 0.29, 1.37), resulting from the large sample size of the EAGLE Study, allows us to conclude that our results are incompatible (chance of <2.5%) with the actual relative risk of lung cancer being 1.37-fold higher in women than in men. The lack of sex-smoking interaction was confirmed in all models adjusting for several potential confounders, stratifying by smoking status, or taking into account possible effect modifiers. These findings were consistent across the 3 main lung cancer subtypes evaluated.

Some case-control studies (7–10), but not all (11–13), have found a higher relative risk of lung cancer among women. On the contrary, most (14–23) but not all (24, 25) cohort studies have found either no sex difference or a higher rate ratio among men. Discrepancies among studies might be attributable to variation in study design, the definition of smoking exposure (which also depends on the accuracy of information collection), estimation of relative risks versus absolute risks, and the use of never smokers or light smokers as the reference category in the analysis (27–31). True sex differences in the underlying risk, such as differences in occupational exposure, secular changes in cigarette smoking and rates of smoking, SHS exposure, and changes in lung cancer itself, may also contribute to the discrepant results (3, 6).

Unlike the majority of previous case-control studies, we were able to assess an accurate individual lifetime smoking history for all of the interviewed subjects. For example, the study by Risch et al. (9), which initiated the hypothesis of higher female susceptibility to tobacco-related lung cancer, relied mainly on next-of-kin exposure assessment of cases. In addition, we addressed this issue in a modern, developed social context where smoking by women was no longer stigmatized, making a sex-specific response bias unlikely. In addition, we accounted for several potential confounders, including different smoking features between the sexes (e.g., inhalation depth, type of tobacco, percentage of each cigarette smoked), nicotine dependence, SHS exposure, and work-related exposure to lung carcinogens, that could affect the baseline risk among never smokers in a sex-specific way.

Our findings are consistent with the majority of previous prospective studies (14–16, 18–23), including the large recent cohort study conducted by Freedman et al. (17). Notably, the latter study had a less accurate assessment of smoking exposure and lacked information on age at smoking initiation, which prevented calculation of smoking duration and thus pack-years.

Examining the previous studies (7–26), the frequency of never smoking among cases was always higher in women than in men, even with higher sex disproportion than we had in our study (e.g., 2 large multicenter European case-control studies found 31.8% vs. 2.1% (11) and 29.6% vs. 1.9% (13) for women and men, respectively). Additionally, the prevalence of current smoking in our study base was not dissimilar to that reported for the same time period in Europe (about 40% among males and 18% among females) (36), in Italy (about 29% and 22%, respectively) (37), or in northern Italy, where the Lombardy region is located (about 27% and 19%, respectively) (38).

In our study, the analyses restricted to the main lung cancer histological types showed no positive female sex-smoking interaction, in accordance with most previous case-control and cohort studies, with a few exceptions (9, 17).

Our study had several key strengths: enrollment of incident cases and randomly sampled population controls; participation rates of 86.6% among cases and 72.4% among controls; and face-to-face collection of detailed information with a structured questionnaire by trained interviewers.

Table 4. Cumulative Exposure to Cigarette Smoking and Associated Odds Ratios for Lung Cancer Among Former Smokers and Current Smokers, by Sex, the EAGLE Study, Lombardy, Italy, 2002–2005

Exposure Measure	Cigarette Smoking Exposure								Odds of Lung Cancer							
									Former Smokers				Current Smokers			
	Women				Men				Women		Men		Women		Men	
	Cases		Controls		Cases		Controls									
	No.	%	No.	%	No.	%	No.	%	OR[a]	95% CI	OR[a]	95% CI	OR[b]	95% CI	OR[b]	95% CI
Categorical variable, pack-years																
Never smoker	103	25.4	282	56.5	29	1.9	397	24.6								
1–19	87	21.4	147	29.5	118	7.7	464	28.7	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent
20–39	124	30.5	49	9.8	420	27.3	413	25.5	3.1	1.5, 6.4	2.8	2.0, 3.8	5.2	2.8, 9.8	4.2	2.5, 7.0
≥40	92	22.7	21	4.2	967	62.9	341	21.1	4.1	1.0, 17.0	4.7	3.3, 6.6	9.1	4.4, 18.8	13.0	7.7, 21.6
Data not available	0	0	0	0	3	0.2	2	0.1								
$P_{interaction}$ [c]										0.95				0.32		
Continuous variable (log_{10} (1 + pack-years/5))									25.0	6.3, 99.1	14.1	8.4, 23.8	60.9	17.4, 213.0	77.6	37.5, 160.7
Female sex-smoking interaction									0.83	0.27, 2.57			0.78	0.20, 3.07		
$P_{interaction}$ [c]										0.74				0.73		

Abbreviations: CI, confidence interval; EAGLE, Environment and Genetics in Lung Cancer Etiology; OR, odds ratio.

[a] ORs and 95% CIs from unconditional logistic regression models, adjusted for residential area, age, and years since quitting smoking.

[b] ORs and 95% CIs from unconditional logistic regression models, adjusted for residential area and age.

[c] *P* values were calculated from the likelihood ratio test or Wald test for the product of sex and pack-years (pack-years as a categorical or continuous (log_{10} (1 + pack-years/5)) variable, respectively).

Table 5. Cumulative Exposure to Cigarette Smoking and Associated Odds Ratios for Lung Adenocarcinoma Among All Subjects, Former Smokers, and Current Smokers, by Sex, the EAGLE Study, Lombardy, Italy, 2002–2005

Exposure Measure	Cigarette Smoking Exposure								Odds of Lung Adenocarcinoma											
									All Subjects				Former Smokers				Current Smokers			
	Women				Men				Women		Men		Women		Men		Women		Men	
	Cases		Controls		Cases		Controls													
	No.	%	No.	%	No.	%	No.	%	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI	OR[b]	95% CI	OR[b]	95% CI
Categorical variable, pack-years																				
Never smoker	77	35.0	282	56.5	18	3.1	397	24.6	1.0	Referent	1.0	Referent								
1–19	55	25.0	147	29.5	56	9.6	464	28.7	1.3	0.7, 2.2	4.2	2.3, 7.5	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent
20–39	53	24.1	49	9.8	171	29.4	413	25.5	3.8	2.6, 6.5	11.4	6.7, 19.3	2.9	1.1, 7.7	2.6	1.7, 4.1	4.1	1.8, 9.2	3.4	1.7, 6.8
≥40	35	15.9	21	4.2	335	57.6	341	21.1	6.7	3.6, 12.4	23.2	14.0, 38.6	2.6	0.4, 15.2	3.8	2.4, 6.1	7.8	3.1, 19.2	9.2	4.7, 18.2
Data not available	0	0	0	0	2	0.3	2	0.1												
$P_{interaction}$[c]										0.005[d]				0.76				0.47		
Continuous variable (log_{10} (1 + pack-years/5))									6.1	3.9, 9.8	16.8	11.6, 24.2	12.6	2.4, 65.6	9.1	4.6, 17.9	45.5	9.7, 214.5	39.2	15.9, 96.7
Female sex-smoking interaction									0.34	0.19, 0.59			0.63	0.16, 2.40			0.70	0.14, 3.49		
$P_{interaction}$[c]										<0.0001[e]				0.50				0.66		

Abbreviations: CI, confidence interval; EAGLE, Environment and Genetics in Lung Cancer Etiology; OR, odds ratio.

[a] ORs and 95% CIs from unconditional logistic regression models, adjusted for residential area, age, and years since quitting smoking.

[b] ORs and 95% CIs from unconditional logistic regression models, adjusted for residential area and age.

[c] *P* values were calculated from the likelihood ratio test or Wald test for the product of sex and pack-years (pack-years as a categorical or continuous (log_{10} (1 + pack-years/5)) variable, respectively).

[d] Negative female sex-smoking interaction coefficients for all of the pack-year categories evaluated.

[e] Negative female sex-smoking interaction coefficient.

Moreover, we had a large sample size that allowed testing for interaction effects and evaluation of risk by histological type. In the main analyses on all lung cancers, the narrow confidence interval for the sex-smoking interaction in ever smokers (95% CI: 0.29, 1.37) indicates that in this study we had sufficient statistical power to detect relatively small (compared with the large smoking main effects) positive or negative interactions. In the analyses within histological subgroups, the power to detect modest-to-high sex-smoking odds ratio interactions was high for adenocarcinoma but not for squamous- and small-cell carcinoma.

Despite our accurate individual exposure assessment, inadequate control for confounders of smoking effect as well as recall bias for smoking are possible in any retrospective study on lung cancer, but this should not be different in males and females.

This analysis, in accord with previous high-quality studies, used logistic regression to estimate the association between pack-years of smoking and risk of lung cancer. In future analyses of sex-specific differences in lung cancer susceptibility, researchers might examine different smoking metrics and alternatives to logistic regression modeling.

In conclusion, our findings do not support the controversial hypothesis that women have a higher relative risk of lung cancer than men from the same amount of tobacco exposure. Thus, as far as lung cancer is concerned, equally vigorous health policy interventions should continue to focus on eliminating smoking in both sexes.

ACKNOWLEDGMENTS

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This work was supported by the Intramural Research Program of the US National Institutes of Health, National Cancer Institute, Division of Cancer Epidemiology and Genetics, Bethesda, Maryland; the Lombardy Region, Direzione Generale Sanità, Environmental Epidemiology Program, Milan, Italy (grants 14013-1/5/2010 and 8956-7/6/2006); the CARIPLO Foundation, Milan, Italy; and the Ministero della Salute and Istituto Nazionale per l'Assicurazione contro gli Infortuni sul Lavoro, Rome, Italy (grant PMS/42/06).

We thank Drs. Hormuzd Katki and Stephanie Kovalchik for their helpful comments.

Conflict of interest: none declared.

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