

# Differences in Lung Cancer Risk Between Men and Women: Examination of the Evidence

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**Background:** Lung cancer incidence is gradually leveling off in U.S. men but is continuing to rise in U.S. women. This increase in U.S. women exceeds that expected from a slower decline of smoking among women. Recent epidemiologic and biochemical studies suggest gender differences in susceptibility to tobacco carcinogens. **Purpose:** We conducted an up-to-date, more in-depth evaluation of our earlier observation of a potential gender difference in relative risk (RR) of lung cancer due to smoking. We added information from several additional case and control subjects and included more precise histologic classification of the cancer type, accurate quantitation of smoke exposure, and adjustments for body size. **Methods:** The present investigation was a part of an ongoing hospital-based, case-control study by the American Health Foundation. It included data from 1889 case subjects (1108 males and 781 females) with lung cancer of squamous/epidermoid, small-cell/oat cell, large-cell, and adenocarcinoma types and 2070 control subjects (1122 males and 948 females) with diseases unrelated to smoking. The case and control subjects were admitted to participating hospitals from 1981 to 1994 and were pair-matched by age, sex, hospital, and the time of hospital admission. Ex-smokers and non-Caucasians were excluded from analyses to avoid confounding. The RRs and 95% confidence intervals were estimated from adjusted odds ratios (ORs) by use of unconditional multiple logistic regression analysis, and statistical significance was determined by two-sided tests. The ORs for major histologic types were estimated at increasing levels of exposure to cigarette smoke. **Results:** Our results indicated that women were more likely to be never-smokers than men, particularly those with the squamous/epidermoid-type cancer (8.3% for women versus 2.9% for men 55 years old or older). Men started smoking earlier, reported inhaling more deeply, and smoked more cigarettes per day than women. In contrast, dose-response ORs over cumulative exposure to cigarette smoking were 1.2-fold to 1.7-fold higher in women than in men for the three major histologic types; these differences were more pronounced for small-cell/oat cell carcinomas and adenocarcinomas than for squamous/epidermoid carcinomas. Adjustments for weight, height, or body mass index did not alter the ORs. **Conclusions:** These results confirm our earlier finding that the ORs for major lung cancer types are consistently higher for women than for men at every level of exposure to cigarette smoke. Furthermore, this gender difference cannot be explained by differences in base-line exposure, smoking history, or body size, but it is likely due to the higher susceptibility to tobacco carcinogens in women. [*J Natl Cancer Inst* 1996;88:183-92]

It is a well-established fact that cigarette smoking is the principal cause of lung cancer in both men and women. The continued higher incidence rates in men reflect their longer and greater exposure to cigarette tar (1).

A pattern has evolved during the past decade in the United States showing that, while lung cancer incidence is leveling off among men, it is continuing to rise at a steady rate among women (2). In fact, there has been a 500% increase in female lung cancer mortality since 1950 (3), surpassing breast cancer as the leading cause of cancer deaths among U.S. women since 1987 (4). At the same time, because of the slower decline in smoking prevalence among women than among men (1), the exposure of women to tobacco carcinogens has gradually approached and, in fact, may soon surpass that of men (2). Consequently, if current trends continue, the lung cancer rates among women are expected to surpass those among men within the next two to three decades.

In light of these trends, recent epidemiologic findings (5-13), which suggest that, dose for dose, women may be more susceptible to tobacco carcinogens than men, are of concern. In fact, the rate of decrease in the gap between male-female lung cancer rates observed during the past three decades is more pronounced than would be expected on the basis of the changing trends in male and female smoking rates alone. Although the issue of a higher susceptibility to tobacco carcinogens by female smokers is still inconclusive, the potential public health consequences of such a phenomenon would be substantial.

Our previous work (8), suggesting that women may be more susceptible to tobacco carcinogens than men, was limited to a broad histologic classification of lung cancer, i.e., Kreyberg I and Kreyberg II types. It is important to further evaluate this finding by using more precise histologic subtypes. In 1985, we started collecting more detailed smoking histories from the study participants. As a result, we now have more precise quantitation of lifelong smoking exposure for each participant based on as many as seven different brands of cigarettes smoked.

Spurred by our initial findings (8) and by the availability of additional data on more case subjects as well as control subjects (with more detailed and precisely quantitated smoking exposures and more defined lung cancer histologies), we conducted an in-depth evaluation of the differences in lung cancer risk between men and women. By reviewing the results of

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See "Notes" section following "References."

relevant laboratory studies and other epidemiologic investigations conducted during the past two decades, we also attempted to evaluate the biological plausibility of our hypothesis of differential gender-related susceptibility to tobacco carcinogens.

## Subjects and Methods

The data were derived from a large, ongoing, hospital-based, case-control study by the American Health Foundation of tobacco-related cancers; this study was described elsewhere (14). The study sample included lung cancer case subjects and control subjects, admitted to 26 participating hospitals in six cities during the period 1981 to 1994. Since ex-smokers represent a heterogeneous group with regard to prior exposure that is difficult to adjust for, we excluded them from the analyses to avoid distorting the exposure measures. We also excluded non-Caucasians, constituting only about 10% of case and control subjects in our data, since their smoking and quitting patterns (15) and their susceptibility to tobacco carcinogens (16) are believed to differ from those of whites and could, therefore, bias the male-female comparisons.

All data were collected using a standardized questionnaire completed by trained interviewers. The questionnaire included detailed questions on demographics, smoking history, medical history, occupational history, and diet.

### Case Subjects

Lung cancer cases are broken down by histologic type as shown in Table 1. In the analyses, we first categorized lung cancer cases into squamous/epidermoid carcinoma (397 male and 165 female case subjects), small-cell/oat cell carcinoma (182 male and 142 female case subjects), and adenocarcinoma (418 male and 384 female case subjects). Alternatively, we also used the broader classification of Kreyberg I (including squamous/epidermoid, small-cell/oat cell, and large-cell carcinomas) (690 male and 397 female case subjects) and Kreyberg II (including adenocarcinoma and bronchiolar and alveolar cell carcinomas) (435 male and 414 female case subjects) (17). The numbers of small-cell/oat cell cancer case subjects were not adequate to be included for the more detailed analyses. Lung cancer case subjects with histologies classified as mixed or other, representing less than 3% of all case subjects, were excluded from the analysis.

### Control Subjects

The control subjects (1122 males and 948 females) were patients who had been diagnosed with non-tobacco-related diseases (i.e., cancers of the reproductive system [prostate, cervix, or ovaries] and digestive system, leukemia and lymphoma, and non-neoplastic diseases such as injuries [fractures or disc problems], kidney or urinary bladder infections, arthritis, hernia, and eye diseases). All disease categories among the control subjects had similar male-female distributions, except in the category of cancers of reproductive organs (30% in females and 8% in males). In addition, more males than females had cancers of the digestive organs (23% of the males versus 13% of the females) and kidney or urinary bladder infections (5% versus 1%), as well as hernia (4% versus 1%). Each control subject was individually matched to a case subject according to age ( $\pm 5$  years), sex, hospital, and time of hospital admission.

Table 1. Distribution of lung cancer by histologic type and gender

Histologic type	No. (%)	
	Males (n = 1156)	Females (n = 831)
Squamous/epidermoid carcinoma	397 (34.3)	165 (19.9)
Small-cell/oat cell carcinoma	182 (15.7)	142 (17.1)
Large-cell carcinoma	111 (9.6)	90 (10.8)
Adenocarcinoma	418 (36.2)	384 (46.2)
Bronchiolar and alveolar cell carcinomas	17 (1.5)	30 (3.6)
Mixed/other cancers	31 (2.7)	20 (2.4)

## Smoking History

The smoking histories included the following information for each brand of cigarettes smoked: number of cigarettes smoked per day, duration of smoking, and cigarette brand, starting with the most recent brand. From 1981 to 1984, the questionnaire provided space to list up to only four different brands of cigarettes; in subsequent years, however, information on up to seven brands of cigarettes could be listed. Whenever in an individual's lifetime the number of different brands smoked exceeded these limits, the earlier brands that could not be listed individually were combined into a single item by averaging their tar yield and cigarettes smoked per day and summing their duration of smoking.

Ever-smokers were defined as those who had ever smoked at least one cigarette per day for 1 year. Current smokers were those who had smoked within the past year. Never-smokers were those who had never smoked cigarettes regularly. Ex-smokers were quitters who had not smoked within the past year.

Data on tar yield for various cigarette brands were obtained from the 1977 and 1988 Federal Trade Register (18) for patients admitted to the hospital from 1981 to 1984 and from 1985 to 1994, respectively. This information was entered into the computer and subsequently linked by a computer program with the appropriate brands of cigarettes smoked in each participant's smoking history.

### Statistical Methods

The cumulative index that measures lifetime exposure to tar through cigarette smoking ( $T$ ) is computed by summing over the different brands smoked ( $B$ ): the products of tar content in milligrams ( $t$ ), the duration (in days) of smoking ( $D$ ), and the number of cigarettes consumed per day ( $C$ ) for that brand ( $i$ ). The result is converted into kilograms:

$$T = \sum^B (t_i \times D_i \times C_i) \times 10^{-6}$$

The relative risks (RRs) for squamous/epidermoid carcinoma and adenocarcinoma, at various levels of exposure, measured in number of cigarettes smoked per day, pack-years, and cumulative tar, were estimated through adjusted odds ratios (ORs) with 95% confidence intervals (CIs), using unconditional multiple logistic regression analysis (19). The unconditional model was chosen because case and control subjects were no longer pair-matched because of the exclusion from our data of quitters, smokers of pipes and cigars, and those with incomplete smoking histories. Adjustment of the ORs was accomplished by including one or more continuously measured covariates, such as age, weight, height, or body mass index (BMI), grouped into quintiles and coded as 0-4, in the logistic regression model. BMI was calculated from body weight and height by use of the following formula:  $BMI = \text{kg}/\text{cm}^2$ . ORs were calculated separately for each level of exposure (coded as 1); never-smokers were the referent category (coded as 0). Alternatively, dose-response ORs were calculated by use of five levels of exposure to cigarette smoke as continuous factors; these levels were coded as 0-4, and 0 represented the referent category. Since the logistic model implies that the logit of risk is a linear function of exposure ( $x$ ), the relative odds for individuals with exposure level  $x_i$  compared with individuals with exposure level  $x_0$  is

$$OR_i = \exp[\beta(x_i - x_0)]$$

Thus, if  $\beta > 0$ , the OR for dose-response estimates the increase in relative odds of disease with each increasing level of exposure.

ORs were considered to be statistically significant if their 95% CIs did not enclose 1.0. The statistical significance of the difference between pairs of ORs was evaluated using the heterogeneity chi-squared test applied to the logarithm of the ORs, as described by Gart (20) and Shee (21).

## Results

### Characteristics of Study Population

The distribution of lung cancer histologic types, by gender, is presented in Table 1. The relative frequency of the squamous/epidermoid-type carcinoma was substantially higher in males than in females (34.3% in males versus 19.1% in females), while adenocarcinoma and bronchiolar and alveolar cell carcinomas had higher relative frequencies among females (46.2%

among females versus 36.2% among males and 3.6% among females versus 1.5% among males, respectively). The distributions of small-cell/oat cell, large-cell, and mixed/other cancers, on the other hand, were similar in the two sexes.

As a result of age matching, approximately 90% of both case and control subjects were 45 years old or older (Table 2). Control subjects tended to be more highly educated than case subjects among both sexes, and males were more likely to be professionals than females. Among both the case and control subjects, more men than women were married, and more women than men were widowed. Further analysis showed the highest proportions of case subjects to be found among divorced/separated men (22.9% for never-smokers and 72.4% for current smokers) and widowed women (16.8% for never-smokers and 77.0% for current smokers).

### Smoking Habits of Study Population

The smoking habits of the study population are shown in Table 3. The gender differences in the smoking habits of our study population were consistent with the hypothesis of a greater susceptibility to lung cancer by females. In general, females with lung cancer had less exposure to cigarette smoke than males with lung cancer. For example, women among both case and control subjects, particularly those aged 55 years or older, were more likely to have never smoked than men. Among case subjects, the highest proportion of those who reported themselves to be never-smokers (compared with ever-smokers) was in women with adenocarcinoma and with age 55 years or older (19% in women versus 10% in men), while those with small-cell/oat cell carcinoma had the lowest frequency of never-smokers in both sexes (0% in males versus 2% in females). In addition, among both case and control subjects, fewer women

than men reported inhaling deeply or inhaling at all, smoking more than 75% of each cigarette, and smoking within 15 minutes of awakening; moreover, compared with men, nearly twice as many women than men started smoking past the age of 20. Finally, both the mean tar yield per cigarette and the mean number of cigarettes smoked per day were higher for men than for women regardless of their case-control status.

### Lung Cancer Risk by Exposure to Cigarette Smoke in Current Smokers

Age-adjusted ORs for squamous/epidermoid carcinoma and adenocarcinoma were calculated at increasing levels of exposure to cigarette smoke. Exposure was expressed as cumulative tar, pack-years, and current number of cigarettes smoked per day. The number of small-cell/oat cell carcinomas (182 males and 142 females) was too low to compute separate RR estimates at individual levels of exposure; therefore, only dose-response ORs were calculated for this third histologic type.

Table 4 lists the ORs for developing squamous/epidermoid carcinoma of the lung in current smokers versus never-smokers. The ORs at each exposure level were consistently higher for women than for men, except at the lowest level of cumulative exposure to tar, although the 95% CIs for individual ORs overlapped between the sexes. The three dose-response ORs were 1.2-fold to 1.5-fold higher for women, and the gender differences were significant over both cumulative exposure to tar (3.2 for women versus 2.1 for men) and number of cigarettes smoked per day (2.9 versus 2.1), but not significant over pack-years of exposure (3.0 versus 2.6).

Because of a higher proportion of never-smokers with adenocarcinoma, the estimated RR for this cancer was consistently lower in both sexes compared with the squamous/epider-

Table 2. Characteristics of study population

Characteristic	Males				Females			
	Squamous/epidermoid carcinoma (n = 397), %	Adenocarcinoma (n = 418), %	Small-cell/oat cell carcinoma (n = 182), %	Controls (n = 1122), %	Squamous/epidermoid carcinoma (n = 165), %	Adenocarcinoma (n = 384), %	Small-cell/oat cell carcinoma (n = 142), %	Controls (n = 948), %
Age, y								
<45	6.6	14.1	5.5	10.6	6.7	10.2	7.7	10.0
45-54	22.2	24.6	22.0	18.5	27.3	26.8	21.1	21.4
55-64	40.3	38.0	47.8	39.0	29.7	32.8	45.8	35.9
≥65	31.0	23.2	24.7	31.8	36.4	30.2	25.4	32.7
Marital status								
Single	7.8	8.6	6.6	8.0	9.1	5.5	4.9	8.0
Married	74.8	79.0	73.1	81.0	53.3	63.5	62.7	61.0
Separated/divorced	9.8	8.6	14.3	6.8	9.7	10.7	11.3	9.5
Widowed	7.6	3.8	6.0	4.2	27.9	20.3	21.1	21.5
Education, y								
<12	34.3	25.7	33.5	21.0	18.8	18.5	30.3	19.5
12	28.8	25.5	36.3	27.1	46.7	47.4	38.7	41.8
13-16	25.5	34.1	27.5	32.0	28.5	28.1	28.2	29.2
>16	11.4	14.7	2.7	19.9	6.1	6.0	2.8	9.6
Occupation								
Professional	27.0	36.1	22.5	40.1	17.0	13.3	14.1	21.6
Skilled	44.8	43.5	47.3	41.9	47.9	43.8	42.3	40.8
Unskilled	28.2	20.3	30.2	18.0	9.1	13.5	22.5	12.9
Housewife	—	—	—	—	26.1	29.4	21.1	24.7

**Table 3.** Smoking habits of study population

	Males				Females			
	Squamous/ epidermoid carcinoma (n = 397), %	Adenocarcinoma (n = 418), %	Small-cell/ oat cell carcinoma (n = 182), %	Controls (n = 1122), %	Squamous/ epidermoid carcinoma (n = 165), %	Adenocarcinoma (n = 384), %	Small-cell/ oat cell carcinoma (n = 142), %	Controls (n = 948), %
% who never smoked								
Age <55 y	0.9	9.7	0.0	45.9	5.4	8.5	0.0	61.4
Age ≥55 y	2.9	10.0	0.0	55.3	8.3	19.0	3.0	75.4
Inhalation								
Never	4.2	1.9	3.9	8.2	8.6	5.0	6.5	12.8
Slightly	7.0	5.1	4.5	14.5	6.5	10.4	15.9	15.8
Moderately	47.1	56.2	56.7	48.8	53.9	54.9	39.8	52.7
Deeply	41.9	37.1	35.3	28.5	30.9	29.7	34.8	18.5
Proportion of cigarette smoked								
All	33.6	29.2	38.5	25.9	29.3	31.3	31.4	29.6
Less than half	26.7	31.1	23.5	30.3	25.3	30.0	30.0	36.9
First cigarette after awakening								
<15 min	62.1	53.5	56.7	42.8	62.1	52.8	57.7	34.9
≥15 min	37.9	46.5	43.3	57.2	37.9	47.2	42.3	65.1
Age started smoking								
≤17 y	67.6	64.1	59.3	56.6	47.1	46.0	49.6	33.1
18-20 y	21.0	23.5	29.4	26.1	32.0	34.7	27.3	34.2
≥21 y	11.4	12.4	11.3	17.2	20.9	19.3	23.0	32.7
Tar yield per cigarette								
Mean	14.7	14.6	14.6	14.3	14.1	13.7	13.4	13.2
Standard deviation	4.8	5.0	5.8	5.0	4.4	4.9	5.5	4.9
Cigarettes smoked per day								
Mean	30.7	30.0	30.0	25.3	26.2	24.2	26.4	19.2
Standard deviation	11.8	12.7	11.0	11.2	11.0	9.8	10.0	9.7

**Table 4.** Odds ratios for lung cancer in current smokers versus never-smokers: squamous/epidermoid carcinoma\*

Exposure measure	Males				Females				Female odds ratio/ male odds ratio
	No. of cases	No. of controls	Odds ratio†	95% confidence interval	No. of cases	No. of controls	Odds ratio†	95% confidence interval	
Tar, kg									
0	8	476	1.0	—	12	673	1.0	—	
1-2	72	141	33.1	15.4-71.0	45	146	24.5	12.0-49.7	
3-5	85	140	36.8	17.3-78.3	53	81	38.5	19.5-76.0	
6-8	85	95	54.3	25.4-116.2	30	30	56.2	26.2-120.5	
≥9	124	92	81.5	38.3-173.2	20	10	129.3	47.3-353.2	
Dose-response			2.1	1.9-2.3			3.2	2.7-3.8	1.5‡
Pack-years									
0	8	476	1.0	—	12	673	1.0	—	
1-19	16	147	6.5	2.7-15.4	13	76	11.9	4.9-28.8	
20-39	58	139	24.1	11.0-52.4	43	105	26.4	13.1-53.4	
40-49	114	141	48.9	22.9-100.7	58	68	48.8	24.9-95.8	
≥50	192	138	82.1	39.5-170.9	39	25	95.2	43.4-209.0	
Dose-response			2.6	2.3-2.9			3.0	2.6-3.5	1.2
Most recent No. of cigarettes smoked per day									
0	8	476	1.0	—	12	673	1.0	—	
1-10	31	235	14.1	7.6-26.4	11	69	9.3	3.9-22.1	
11-20	87	188	16.0	9.5-27.0	52	125	33.0	16.3-66.6	
21-40	169	174	38.9	23.1-65.3	75	68	74.9	37.0-151.5	
≥41	94	49	66.8	36.8-121.3	15	13	85.3	29.5-247.1	
Dose-response			2.1	1.9-2.3			2.9	2.5-3.3	1.4‡

\*Referent group: never-smokers.

†Adjusted for age.

‡Significant at  $P < .05$ .

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moid type, at individual levels of exposure and also for the dose-response (OR = 1.8-2.0 for men and 2.5-2.9 for women) (Table 5). The dose-response OR for women was significantly higher (1.3-fold to 1.6-fold) than for men by all three exposure measures. As with squamous/epidermoid carcinoma, the gender difference in the dose-response OR for adenocarcinoma was greatest when estimated over cumulative exposure to tar.

Similarly, all three dose-response ORs for small-cell/oat cell carcinoma were significantly higher (1.5-fold to 1.7-fold) for women than for men (4.0 for women versus 2.3 for men for tar yield, 3.7 for women versus 2.5 for men for pack-years, and 3.2 for women versus 2.1 for men for number of cigarettes smoked per day). As before, the gender difference in OR was most prominent when estimated over cumulative exposure to tar.

When the category squamous/epidermoid carcinoma was combined with the categories of small-cell/oat cell carcinoma and large-cell carcinoma (Kreyberg I), the gender differences were greater than those for squamous/epidermoid carcinoma alone, and the dose-response ORs were significantly higher for females by all three exposure measures: 1.7-fold higher for tar yield and 1.4-fold higher for both pack-years and number of cigarettes smoked per day (Fig. 1). This is likely to be due to the larger sample sizes and narrower CIs, in addition to the higher ORs of small-cell/oat cell and large-cell carcinomas.

The combination of the category bronchiolar and alveolar cell carcinomas with that of adenocarcinoma (Kreyberg II), due to the higher percentage of never-smokers among case subjects with bronchiolar and alveolar cell carcinomas than among those with adenocarcinoma (7% versus 6% and 24% versus 11% for

males and females, respectively), produced slightly lower ORs than those obtained for adenocarcinoma alone. Nevertheless, despite the higher nonsmoking rates for female case subjects, the gender difference remained statistically significant for all three exposure measures; dose-response ORs were 1.5-fold higher for tar yield and 1.3-fold higher for both pack-years and number of cigarettes smoked per day in women than in men.

Alternatively, we recomputed the ORs listed in Tables 4 and 5 by substituting light smokers for never-smokers as the referent category to reduce the effect of potential differences in base-line exposure to lung carcinogens between males and females. Although the resultant RR estimates computed at individual exposure levels were considerably lower than before, the values of the dose-response ORs and the magnitude of the male-female differences in ORs remained unchanged. Nonetheless, these differences were no longer statistically significant, which is not surprising in light of the reduction in statistical power that resulted from the exclusion of never-smokers from this analysis.

### Effect of Body Weight on ORs for Lung Cancer

As shown in Fig. 2, adjustment for body weight (reported as of 5 years before diagnosis of the current disease) had virtually no effect on either the magnitude or the male-female differences in the ORs for any of the major histologic types of lung cancer examined. Subsequent adjustments for height and body mass index caused similarly minor changes in the ORs at individual levels of exposure, while all dose-response ORs remained unchanged by any of these adjustments.

Table 5. Odds ratios for lung cancer in current smokers versus never-smokers: adenocarcinoma\*

Exposure measure	Males				Females				Female odds ratio/ male odds ratio
	No. of cases	No. of controls	Odds ratio†	95% confidence interval	No. of cases	No. of controls	Odds ratio†	95% confidence interval	
Tar, kg									
0	38	476	1.0	—	58	673	1.0	—	
1-2	85	141	7.1	4.6-11.0	122	146	11.6	7.8-17.1	
3-5	80	140	6.8	4.4-10.5	101	81	13.9	9.3-20.9	
6-8	93	95	12.4	8.0-19.2	66	30	25.4	15.2-42.2	
≥9	99	92	14.7	9.4-23.1	26	10	33.2	15.0-73.3	
Dose-response			1.8	1.7-2.0			2.9	2.5-3.3	1.6‡
Pack-years									
0	38	476	1.0	—	58	673	1.0	—	
1-19	29	147	2.4	1.4-4.1	37	76	6.8	4.1-11.4	
20-39	71	139	5.6	3.6-8.7	99	105	11.2	7.5-16.8	
40-49	127	141	11.6	7.7-17.6	122	68	21.4	14.3-32.2	
≥50	145	138	13.8	9.2-20.9	66	25	32.7	19.0-56.2	
Dose-response			2.0	1.8-2.2			2.5	2.3-2.8	1.3‡
Most recent No. of cigarettes smoked per day									
0	38	476	1.0	—	58	673	1.0	—	
1-10	25	235	4.4	2.5-7.6	26	69	4.5	2.7-7.7	
11-20	105	188	7.2	4.9-10.4	127	125	14.2	9.6-20.9	
21-40	166	174	12.1	8.4-17.4	142	68	27.2	17.8-41.6	
≥41	76	49	19.3	12.0-30.3	31	13	34.3	16.2-72.5	
Dose-response			1.8	1.7-1.9			2.5	2.2-2.8	1.4‡

\*Referent group: never-smokers.

†Adjusted for age.

‡Significant at  $P < .05$ .

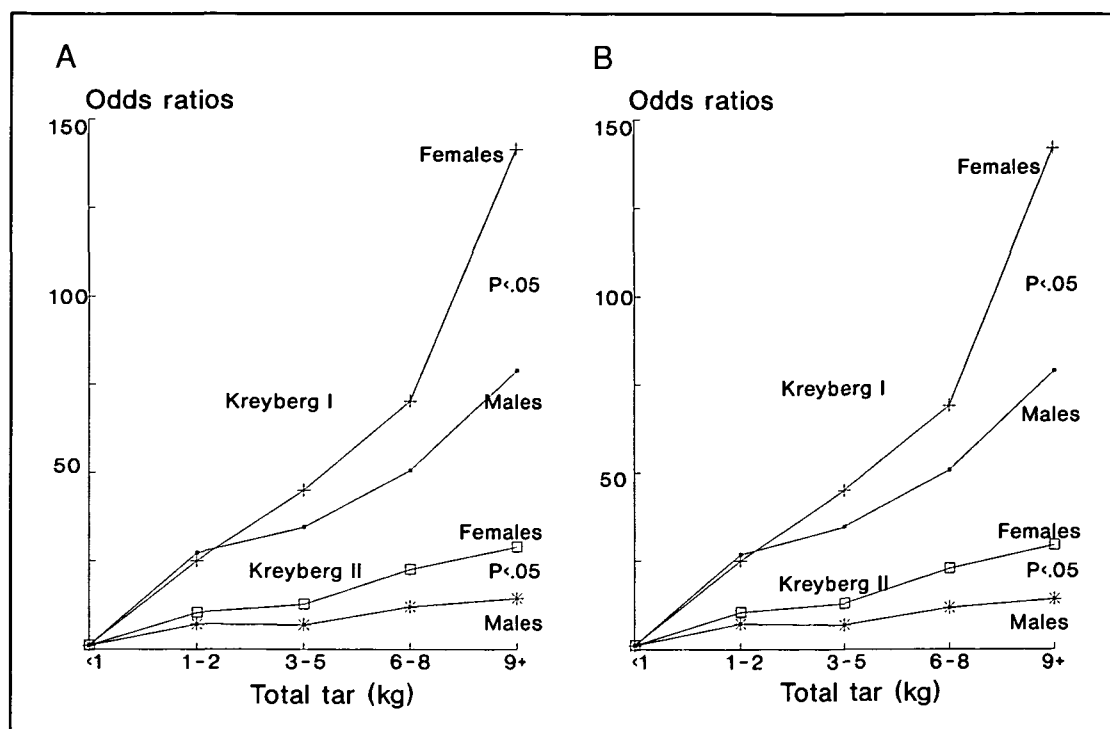


Fig. 1. Sex-specific odds ratios for Kreyberg I-type (690 male and 397 female case subjects) versus Kreyberg II-type (435 male and 414 female case subjects) lung cancer, adjusted for age only (A) or adjusted for age plus prediagnostic body weight (B). *P* values are based on overall gender differences in odds ratios.

## Discussion

The aim of this more detailed re-evaluation of our data was to further explore the feasibility of the hypothesis of a gender difference in the RR for lung cancer, as our earlier results (8) suggested. The current study included 616 additional case subjects and an equivalent number of control subjects accrued since 1988, and the histologic classifications were no longer limited to Kreyberg I and II. Finally, to avoid biasing the RR estimates (15,16), we decided to exclude the small number of non-Caucasians from our data.

The results of the present study essentially confirm our initial finding that, given the same level of lifelong exposure to cigarette smoke, women had an approximately 1.5-fold higher estimated RR of developing lung cancer than men (8). Furthermore, the gender difference in estimated RR (*a*) was statistically significant for all three major histologic types of lung cancer, although slightly greater for adenocarcinoma and small-cell/oat cell carcinoma than for squamous/epidermoid cancer; (*b*) increased with increasing levels of lifelong exposure to cigarette smoke; (*c*) was most pronounced when differences in Federal

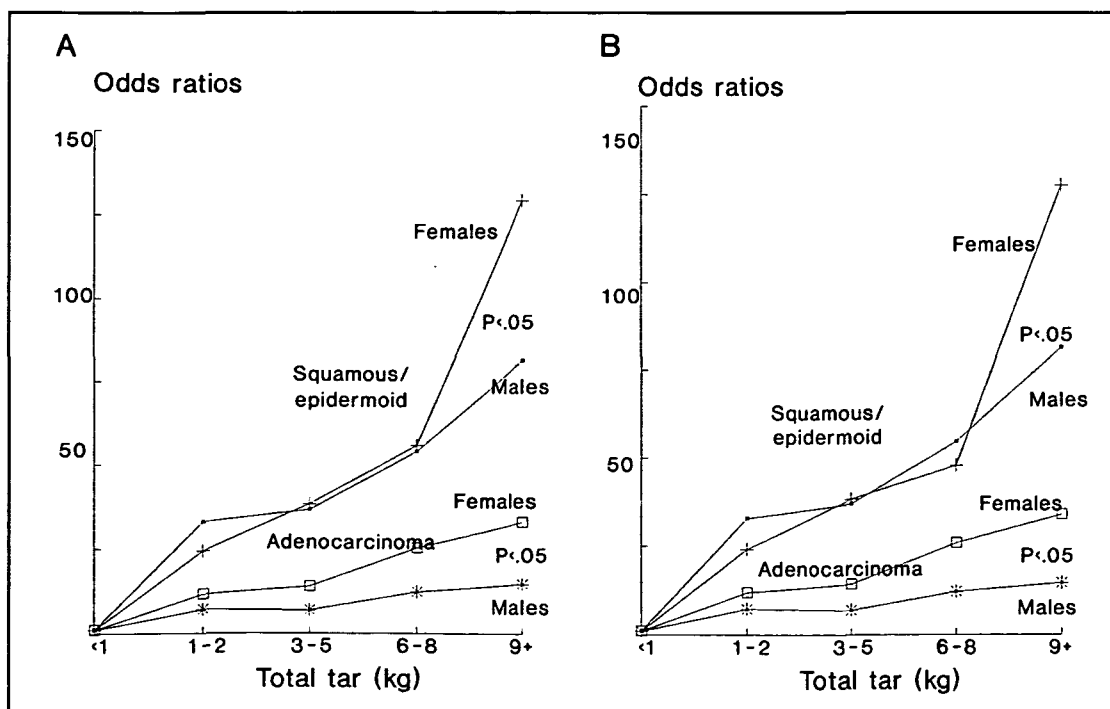


Fig. 2. Sex-specific odds ratios for squamous/epidermoid carcinoma of the lung (397 male and 165 female case subjects) versus adenocarcinoma of the lung (418 male and 384 female case subjects), adjusted for age only (A) or adjusted for age plus prediagnostic body weight (B). *P* values are based on overall gender differences in odds ratios.

Trade Commission-reported tar yield, combined with duration of smoking and number of cigarettes smoked per day, were included in the comparison; and (d) was unrelated to differences in body weight and height.

Our results further suggest that the apparent higher RR for lung cancer in women may apply to nonsmokers as well, since the proportion of never-smoking lung cancer patients was more than twice as high in women than in men—surpassing the gender difference in smoking prevalence during the past several decades. All of these findings suggest that women may have a greater susceptibility to the effects of lung carcinogens than men.

### Potential Confounders and Biases

We considered the possibility that the observed gender differences may be due to unequal base-line exposures, differences in body size, or incorrect estimates of exposure to tobacco smoke.

(a) **Differences in base-line exposure.** It has been suggested that the lower ORs due to smoking in males may actually be the result of men's higher base-line risk caused by occupational exposures to lung carcinogens (22,23). On the contrary, both our current and previous (8) results, as well as results obtained by McDuffie et al. (7), showed that women with lung cancer were two to three times more likely to have never smoked than men. This finding suggests that women, not men, may have a higher base-line risk. Because of the higher smoking rates of men, non-smoking married women are more likely to have been exposed to passive smoke than their male counterparts. In fact, in our data, the highest frequency of lung cancer cases occurred among widows, regardless of their smoking status; this finding raises the possibility of smoking-related deaths among their heavily smoking former spouses and consequent passive smoking by the widows themselves. Thus, given a greater base-line exposure, the dose-response ORs over active smoking should be lower, rather than higher, in women. In fact, we found women to have a higher estimated RR due to smoking, regardless of whether light smokers or never-smokers were used as the reference category.

(b) **Male-female differences in body size.** It is recognized that lung cancer risk and smoking are both inversely related to obesity (24) and that women tend to be smaller than men. However, adjustments for body weight and size did not alter the differences in ORs between males and females, indicating that the association between lung cancer and body size could not account for the observed gender differences in RR.

(c) **Biased or incorrect measures of smoking exposure.** We further considered the possibility that, while women smoked fewer cigarettes and chose cigarettes of lower tar and nicotine yield, their exposures to tobacco carcinogens may have been underestimated as a result of smoking behavior affecting the actual amount of tar inhaled. In fact, the lack of a negative association between the number of cigarettes smoked per day and the Federal Trade Commission-reported tar and nicotine yield in both sexes failed to provide evidence of nicotine compensation through smoking. Furthermore, in both the case subjects and the control subjects, we found that men tended to inhale more deeply and to have started smoking at an earlier age than women.

Thus, since we did not adjust for depth of inhalation and age at smoking onset, the RR for women, compared with that for men, due to smoking was likely to have been underestimated by our results.

Nevertheless, the amount of tar inhaled is also influenced by puff frequency and puff volume (25), both of which may differ by gender. Work is currently under way at the American Health Foundation to determine the ratio of actual to Federal Trade Commission-reported milligrams of tar inhaled by nicotine yield, race, and sex. When this information becomes available, we will include it in our index of lifelong exposure to cigarette tar.

An additional possible source of error in our exposure estimates was recall bias, since it is impossible to obtain direct estimates of the validity of information regarding past smoking habits. Nonetheless, based on measures of reproducibility obtained through regular monthly re-interviews conducted on random samples of 10% of the new study participants, the level of agreement for responses related to smoking was found to be high (correlation coefficient = .93) (26), which may be construed as an indirect indication of high validity.

The accuracy of our measure for lifelong exposure to tar is somewhat compromised by the fact that the tar yields are currently those reported in the 1977 and 1988 Federal Trade Commission reports (18). In fact, since tar yields within specific cigarette brands have continually decreased during the past three decades (27), the exposure of long-term, heavy smokers tends to be underestimated by this measure. Nevertheless, since the majority of long-term, heavy smokers are men, this bias is expected to diminish, rather than to inflate, women's RRs due to smoking.

An additional limitation is that, in the past, we did not have the lung cancer histologies verified by an independent review panel; instead, we simply recorded the individual pathologists' classifications in our data. However, the likelihood of bias is reduced by the fact that the frequencies of the various histologies for both sexes are consistent with those published by the Surveillance, Epidemiology, and End Results (SEER) Program<sup>1</sup> during the same period (28).

### Relevant Findings by Other Investigators

During the past decade, several studies (5-13) have found a greater susceptibility to lung carcinogens by women smokers. Notably, a study by Risch et al. (10) reported male and female risk ratios that were remarkably consistent with our earlier (8) and current results. In fact, a gender difference in estimated RR was observed for all major histologic types by most investigators (5,8,10), with the exception of Osann et al. (11), who found this difference only for small-cell carcinoma. Furthermore, in agreement with our RR estimates obtained over various levels of current number of cigarettes smoked per day, higher RRs for women were observed even without adjustment for tar yield (5-13) and duration of exposure (8,9). Thus, since men are more likely to be long-term, heavy smokers than women, this implies that some of these studies may have underestimated the actual gender difference in RR estimates.

Begg et al. (12) provided a broader indication of a female-male difference in susceptibility to tobacco carcinogens. Their

results suggested that women may have higher RRs for developing second primaries of most smoking-related cancers, including those of the esophagus, urinary bladder, and kidney, in addition to lung.

On the other hand, some studies either found a lower RR in women compared with men (29) or did not observe a gender difference in RR for lung cancer at all (30,31). These include three major cohort studies: the American Cancer Society's Second Cancer Prevention Study (29), the British Physicians Study (30,31), and an ongoing study conducted by the U.S. National Cancer Institute (32). The first of these studies (29) found higher ORs for male current smokers and ex-smokers than for female current smokers and ex-smokers, while the other two studies (30,31) found no difference in RR between the sexes. However, because men have traditionally smoked more than women, a higher susceptibility for females could well have been camouflaged by their lower exposures. In fact, none of these studies adjusted for duration of smoking or tar yield in their RR estimates. In addition, the RRs for men are likely to have been inflated by a lower proportion of never-smokers among male lung cancer case subjects. Nevertheless, if women are, in fact, more susceptible to lung cancer than men, this should become increasingly evident as gender differences in smoking exposure continue to diminish.

### Potential Biological Explanations

The biological plausibility of a higher susceptibility to tobacco carcinogens in women is supported by several laboratory investigations. These investigations are related to nicotine metabolism, cytochrome P-450 enzymes, and hormonal factors.

(a) **Gender differences in nicotine metabolism.** Clinical studies (33,34) have indicated that the total plasma clearance of nicotine, normalized for body weight, is lower in women than in men. Furthermore, Hecht and Hoffmann (35) showed that nicotine can be a precursor for tobacco-specific carcinogens. Clinical observations of a lower nicotine metabolism by women are supported by several studies on rats (36-38) and by one study on stump-tailed macaques (39). However, there is at least one study (40), conducted on a group of smokers in the U.K., that found no gender difference in nicotine exposure.

(b) **Male-female variations in cytochrome P-450 enzymes.** Recent evidence shows that cytochromes P-450 1A1, 1A2, 2E1, 2A6, and perhaps other cytochrome P-450 enzymes in human liver are involved in the bioactivation of genotoxic components in cigarette smoke condensate, including polycyclic aromatic hydrocarbons, certain nitrosamines, and aromatic amines (41). Thus, one factor modulating the development of carcinogenesis is believed to be interindividual differences in the activity of these enzymes (41). In fact, as early as 1974, Kato (42) suggested that "... the sex difference in the oxidation of drugs by liver microsomes is due mainly to the higher binding capacity of cytochrome P-450 of male rats." In an even earlier study published in 1967, Schenkman et al. (43) noted that "... microsomes isolated from the livers of male rats had twice the magnitude of substrate (hexobarbital and aminopyrine) binding than did microsomes isolated from the livers of female rats." Consequently, differences in the activity of these enzymes

could also influence the lung cancer susceptibility in men and women.

In more recent years, evidence has been accumulating that cytochrome P-450 in liver microsomes plays a central role as a drug-metabolizing enzyme and that there are sex-dependent differences in the properties of this enzyme (44). For example, in comparing cytochrome P-450 isozyme-selective bioactivation of 1,1-dichloroethylene in the lungs of female and male mice, Lee and Forkert (45) found that CYP2E1-dependent *p*-nitrophenol hydroxylation was significantly higher in microsomes from females than from males, suggesting that females may be at slightly greater risk for 1,1-dichloroethylene-induced pneumotoxicity. Other investigators observed that lung microsomes from male rats had increased activity of P4502C11 (46); that 1-benzylimidazole produced a statistically significant increase in P-450 2B1/2 in male rats, but not in female rats (47); that the levels of cytochrome P-450 enzymes differ in the hair follicles of men and women (48); and that castration of male rats markedly reduced microsomal sulfamethazine hydroxylation rates, suggesting that the male-specific P-4502C11 enzyme plays an important role in the hydroxylation of sulfamethazine (49).

In addition, Ryberg et al. (50) found that the DNA adduct levels were higher in female than in male lung cancer patients after adjustment was made for smoking dose and that "... patients with high adduct levels generally had shorter duration of smoking and/or lower smoking dose before the clinical onset of the disease." This observation suggests that women are exposed to higher levels of nicotine than men and thus may have a greater RR for tobacco-induced lung cancer.

(c) **Effect of hormones on tumor development.** Support for the hypothesis that endogenous and exogenous hormones play an important role in carcinogenesis comes from both epidemiologic observations and basic research findings. In a large-scale epidemiologic cohort study, Adami et al. (51) reported a slightly, although not significantly, elevated RR (RR = 1.3; 95% CI = 0.9-1.7) for lung cancer in women who received estrogen replacement therapy, but no allowance was made for histologic type or smoking. Gao et al. (52) reported short menstrual cycles to be associated with lung cancer risk in Chinese women, although our data do not confirm this. Using data from the American Health Foundation's long-standing case-control study on smoking and lung cancer (also used in the present study), Taioli and Wynder (53) found both an elevated risk due to hormone replacement (OR = 1.7; 95% CI = 1.0-2.5) and a statistically significant synergy between the effects of smoking and estrogen replacement therapy with regard to adenocarcinoma of the lung. We plan to further investigate this association as our data on estrogen replacement therapy continue to accumulate with respect to estrogen exposure. Finally, in our current results, women 55 years old or older with lung cancer, particularly with adenocarcinoma, were nearly twice as likely to be never-smokers than younger women with lung cancer, while no comparable age-related difference in smoking was found either among male lung cancer case subjects or among female control subjects (Table 3).

That sex hormones affect cytochrome P-450 was already suggested in 1974 by Kato (42), who stated: "The content of



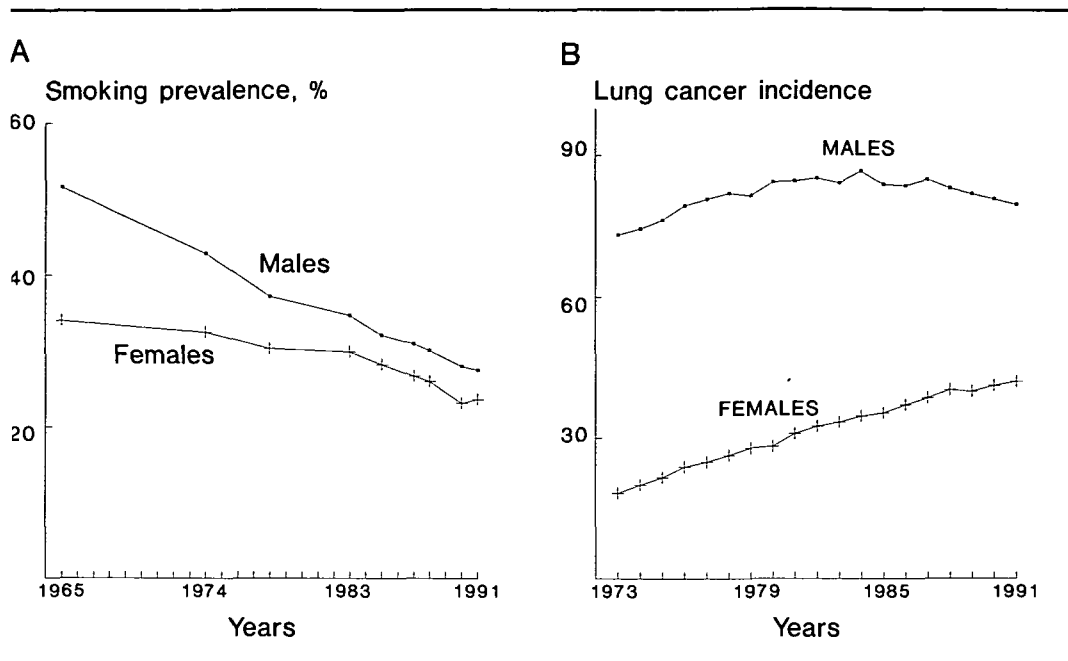


Fig. 3. A) Current cigarette smoking prevalence in U.S. males and females 18 years old or older. Source: Centers for Disease Control and Prevention, National Center for Health Statistics; data from the National Health Interview Survey (1). B) Surveillance, Epidemiology, and End Results Program incidence rates for invasive lung and bronchus cancers for all U.S. males and females (2). Rates are per 100 000 and are age adjusted to the 1970 U.S. standard population.

cytochrome P-450 in microsomes is increased 20-30% by rogen,” and “. . . castration of male rats decreases both the elimination of some drugs and the binding capacity of cytochrome P-450 for these compounds.” In addition, various hormones have been shown to be involved in the induction and development of lung tumors. For example, repeated injections of growth hormone into female rats induced lymphomas of the lung, and injections of estradiol into guinea pigs induced lung adenomas, while concomitant administration of dexamethasone, cortisone, progesterone, and testosterone inhibited estrogen-induced lung tumorigenesis in guinea pigs (1). Thus, estrogen-induced lung tumors in female guinea pigs are hormone responsive; consequently, the levels of sex hormones and their influence on the metabolism of tobacco carcinogens are likely to affect the susceptibility to lung cancer in males and females.

In summary, our present results agree with the hypothesis that, dose for dose, females are more susceptible to the effects of tobacco carcinogens than males. Furthermore, this difference does not appear to be the result of external factors, such as occupational exposure or smoking behavior, and it does not seem to be related to body size or lung size. A more plausible explanation may be variations in physiologic mechanisms, such as differences in metabolic activation and detoxification of lung carcinogens. In view of the continued high smoking prevalence and the growing incidence of lung cancer among women (Fig. 3), it is important to accumulate evidence of their increased susceptibility to tobacco carcinogens, effective programs for smoking prevention and cessation must have a high priority on our agenda for women's health issues.

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## Notes

<sup>1</sup>Editor's note: SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.

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