

Risk of Squamous Cell Carcinoma and Adenocarcinoma of the Lung in Relation to Lifetime Filter Cigarette Smoking

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BACKGROUND. Over the past few decades, the incidence of adenocarcinoma (AC) of the lung increased much more rapidly than that of squamous cell carcinoma (SCC) in men and women. During this time period, filter cigarettes with substantially reduced “tar” and nicotine yields in the smoke came to dominate the market.

METHODS. The risk of SCC and AC in lifelong smokers of filter cigarettes relative to lifelong nonfilter cigarette smokers was assessed in a case-control study performed between 1977 and 1995 with 2292 lung carcinoma patients and 1343 hospital controls who were current smokers.

RESULTS. Odds ratios (OR) for SCC in male and female subjects who had smoked filter cigarettes exclusively during their lives were slightly reduced relative to lifetime nonfilter cigarette smokers in men (OR = 0.8; 95% confidence interval [CI], 0.5–1.2), and significantly reduced in women (OR = 0.4; 95% CI, 0.2–0.8). No reduction in risk was observed for AC of the lung in men or women.

CONCLUSIONS. Evidence that the increasing predominance of AC over SCC may be due in part to the reduced risk of SCC (but not AC) associated with lifelong filter cigarette smoking is strongest in women; for men, further studies that include larger numbers of lifetime filter smokers are needed to confirm this finding. A lack of protection against AC from low yield filter cigarettes may result from smokers’ “compensating” with deeper and more frequent inhalation, thereby increasing delivery of carcinogens to the peripheral lung. The smoke of modern cigarettes also contains higher concentrations of nitrosamines that primarily produce AC. *Cancer* 1997;80:382–8. © 1997 American Cancer Society.

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Most of the carcinogens in tobacco smoke reside in the “tar.”¹ Since midcentury, the sales-weighted average yield of “tar” declined in the U.S. by approximately 60%.² According to standardized machine smoking of cigarettes used by the Federal Trade Commission (FTC) to determine the smoke yields of nicotine and “tar” for all brands of cigarettes manufactured in the U.S., the sales-weighted average yields per cigarette until the mid-1960s were in the range of 1.5–2.7 mg of nicotine and 22–35 mg of “tar.” For the most recent 15-year period, the FTC reported sales-weighted average nicotine and “tar” yields of 0.90–0.95 mg and 12–14 mg, respectively.² Today, approximately 25% of all cigarettes consumed in the U.S. deliver ≤ 0.8 mg nicotine, and approximately 50% of cigarettes yield 0.9–1.2 mg of nicotine, whereas the remaining 25% of brands deliver ≥ 1.2 mg of nicotine.^{3,4}

The lower “tar” emissions have been primarily accomplished by utilizing efficient filter tips and highly porous cigarette paper, and by changing the composition of the tobacco blend. Bioassays in labora-

tory animals conducted during the 1960s and 1970s showed that "tars" of contemporaneously smoked cigarettes had lower carcinogenic activity per gram than earlier cigarettes.⁵⁻⁷ Therefore, it was anticipated that the risk of lung carcinoma in smokers of cigarettes with lower "tar" yields would eventually decline relative to risk in smokers of medium or high "tar" brands.

Indeed, reports from the authors' group in 1970,⁸ 1976,⁹ 1977,¹⁰ and 1979,¹¹ as well from other investigators,¹²⁻¹⁵ confirmed that smokers who switched from nonfilter to filter cigarettes had lower lung carcinoma risks compared with those who continued to smoke nonfilter cigarettes. The earlier studies were based on patient populations whose lifetime smoking histories were dominated by nonfilter cigarettes that had significantly higher "tar" emissions than those commonly smoked during recent decades.¹³ However, studies of lung carcinoma patients diagnosed during the past 10-15 years have failed to consistently show a "protective" effect of filters.¹⁶⁻¹⁹ That the incidence of adenocarcinoma (AC) has been increasing much more rapidly than that of squamous cell carcinoma (SCC) in men and women in the U.S.,²⁰ even while "tar" and nicotine yields were declining, suggests the need to examine the risk for lung carcinoma by histologic type in relation to long term use of nonfilter and filter cigarettes.

MATERIALS AND METHODS

This study used data collected from a multicenter hospital-based case-control study of risk factors for lung carcinoma that was initiated in 1977. The methodology has been previously described in detail.^{10,21} In brief, after a consent form approved by the local Institutional Review Board was signed, patients with newly diagnosed lung carcinoma were interviewed by trained personnel in New York and in other U.S. cities. Structured questionnaires were used to obtain detailed smoking histories and data on other lifestyle habits. A complete history of each patient's smoking habits was taken that included the name of each brand and the years during which it was smoked. The histologic types of lung carcinoma were obtained from surgical pathology reports or cytologic findings. The control patients were admitted to the same hospitals for conditions unrelated to cigarette smoking. A frequency matching procedure was based on the case patient's age (± 5 years), gender, hospital, and the date of admission (± 2 months).

Cigarette type was characterized according to whether subjects smoked nonfilter cigarettes exclusively, had switched from smoking nonfilter to filter cigarettes, or had smoked filter cigarettes exclusively.¹¹ There were no patients who switched from smoking filter to nonfilter cigarettes. This categorization was

chosen because throughout the past 40 years, with few exceptions, filter cigarette brands have had lower levels of "tar" and nicotine than nonfilter brands. This has remained consistent, even as the sales-weighted average "tar" and nicotine levels of both types of cigarettes gradually declined over the years.² Therefore, categorizing cigarettes as filter or nonfilter brands is tantamount to qualitatively dichotomizing by "tar"/nicotine yield.

Odds ratios (ORs) associated with smoking filter cigarettes were calculated using unconditional logistic regression, adjusting for age, education, and number of cigarettes smoked per day, in separate strata of gender and histologic type of tumor. For these calculations, the reference group was composed of lifetime smokers of nonfilter cigarettes.

Because OR estimates for the two histologic outcomes were based on a common set of control patients, it is inappropriate to use confidence intervals to test whether the ORs for persons with the same filter usage history (e.g., lifetime filter cigarette smokers) differ by histologic type. Wald's chi-square statistic was used to test differences between the regression parameters, utilizing the variance-covariance matrix obtained from a polytomous logistic regression model.²²

RESULTS

Between 1977 and 1995, a total of 1442 male and 850 female lung carcinoma patients with SCC or AC who were current smokers were interviewed, along with 876 male and 467 female controls who were also current smokers (Table 1). The ratio of AC to SCC was approximately 1:1 among the males and 2:1 among the females. The proportion of males who smoked filter cigarettes exclusively was 8.5% of SCC cases, 12.4% of AC cases, and 13.9% of controls. Prevalence of lifetime filter cigarette smoking among women was 20.3% of SCC cases, 27.8% of AC cases, and 33.8% of controls.

Histologic type was strongly associated with age and less strongly with education. AC occurred nearly twice as frequently as SCC among both men and women younger than age 45 years who were current smokers, compared with current smokers in older age groups; 11.2% of the men with AC were diagnosed before age 45 years compared with 6.6% of men with SCC (OR = 1.8; $P < 0.01$) and 12.5% of women with AC were younger than age 45 years compared with 7.6% of women with SCC (OR = 1.8; $P < 0.05$).

Individuals with AC had on average slightly more years of education than those with SCC (12.6 years vs. 11.9 years for men; 12.5 years vs. 12.1 years for women). There were no differences in the distribution of these lung carcinoma cell types between African American and white subjects, and there were no differ-

TABLE 1
Distribution of Lung Carcinoma Cases and Controls According to Gender, Histologic Type of Carcinoma, and Lifetime Filter Cigarette Smoking. Current Smokers only. American Health Foundation, 1977–1995. (Number of Subjects in Parentheses.)

	Squamous cell carcinoma	Adenocarcinoma	Controls
Males	(730)	(712)	(876)
		Percent	
Lifetime filter	8.5	12.4	13.9
Switched from nonfilter to filter	69.7	68.7	67.2
Lifetime nonfilter	21.8	19.0	18.8
Females	(281)	(569)	(467)
Lifetime filter	20.3	27.8	33.8
Switched from nonfilter to filter	68.0	66.6	59.7
Lifetime nonfilter	11.7	5.6	6.4

TABLE 2
Average Age and Smoking Characteristics of Study Subjects by Gender, Filter Cigarette Usage, and Histology. Current Smokers only. American Health Foundation, 1977–1995.

	Filter usage	Males			Females		
		Squamous cell carcinoma	Adenocarcinoma	Controls	Squamous cell carcinoma	Adenocarcinoma	Controls
Average age (yrs) at diagnosis	LF	48.6	49.4	46.2	52.8	50.6	51.8
	SW	59.4	58.0	58.1	60.7	58.8	57.9
	NF	60.3	57.7	56.8	61.6	59.8	58.8
Average age (yrs) began smoking	LF	17.7	18.9	21.0	19.8	19.8	23.3
	SW	16.4	16.4	17.2	18.2	18.1	19.2
	NF	15.9	16.0	16.4	18.2	18.8	21.2
Average no. cigarettes smoked per day	LF	32.8	27.8	22.8	27.1	27.8	18.8
	SW	34.4	33.6	26.0	30.8	28.3	21.8
	NF	33.3	33.9	26.6	28.9	26.6	19.9
Average no. years smoked cigarettes	LF	30.5	29.4	24.2	32.7	30.4	27.4
	SW	42.6	40.9	39.8	42.0	40.3	37.6
	NF	44.2	41.3	40.1	43.2	41.5	37.5

LF: lifetime filter; SW: switched from nonfilter to filter; NF: lifetime nonfilter.

ences in urban versus rural residence; 55% of both male and female cases with lung carcinoma of either cell type and 55% of controls had lived in large metropolitan areas (> 250,000 persons) for most of their adult lives.

Characteristics of Current Cigarette Smokers

Lifetime filter cigarette smokers (LF), both men and women, were substantially younger than either lifetime nonfilter cigarette smokers (NF) or controls (Table 2). This age difference was reflected in substantially shorter duration of smoking: 13.7 years less for men and 10.5 years less for women with SCC who were LF smokers compared with NF smokers of the same

gender. Generally, the NF smokers began to smoke at earlier ages than did the LF smokers (4.6 years earlier for male controls, 2.1 years earlier for female controls).

The ORs and 95% confidence intervals (CI) according to duration of filter cigarette smoking for the three filter usage categories are presented in Table 3. ORs are adjusted for age, education, and number of cigarettes smoked per day. Among current smokers, the critical factor in this table was the extent, if any, to which LF smokers may be at lower risk compared with NF smokers, and specifically whether this effect differs by histologic type of lung carcinoma. The risk of SCC was slightly lower among LF smokers for men (OR = 0.8; 95% CI, 0.5–1.2) and significantly lower for

TABLE 3
Adjusted^a Odds Ratios for Squamous Cell Carcinoma and Adenocarcinoma of the Lung among Current Cigarette Smokers, by Lifetime Filter/Nonfilter Cigarette Consumption. American Health Foundation, 1977–1995.

Males

No. of subjects	Squamous cell carcinoma				Adenocarcinoma			Chi-square ^b
	Controls 876 (%)	Cases 730 (%)	OR	95% CI	Cases 712 (%)	OR	95% CI	
Lifetime nonfilter smoker	18.8	21.8	1.0		19.0	1.0		
Switched	67.2	69.7	0.9	0.7–1.2	68.7	1.0	0.8–1.3	0.4
Lifetime filter smoker	13.9	8.5	0.8	0.5–1.2	12.4	1.0	0.7–1.5	1.0

Females

No. of subjects	Squamous cell carcinoma				Adenocarcinoma			Chi-square ^b
	Controls 467 (%)	Cases 281 (%)	OR	95% CI	Cases 569 (%)	OR	95% CI	
Lifetime nonfilter smoker	6.4	11.7	1.0		5.6	1.0		
Switched	59.7	68.0	0.6	0.3–0.99	66.6	1.2	0.7–2.0	7.0 ^c
Lifetime filter smoker	33.8	20.3	0.4	0.2–0.8	27.8	0.9	0.5–1.7	7.6 ^c

OR: odds ratio; CI: confidence interval.

^a Adjusted for age (continuous), education (three categories), and number of cigarettes per day (three categories).

^b Wald chi-square test for equality of logistic regression coefficients between histologic types.

^c $P < 0.01$.

women (OR = 0.4; 95% CI, 0.2–0.8). ORs for SCC among those who switched from nonfilter to filter cigarettes were intermediate. By contrast, the AC risks were not significantly reduced either for men or for women (OR = 1.0 and 0.9, respectively).

DISCUSSION

These findings support the hypothesis that the wide-scale changes in the incidence of SCC and AC are related to changes in the concentration and type of carcinogens in the smoke of manufactured cigarettes. Since approximately 1970 in the U. S., AC as a percent of all lung carcinomas has nearly doubled in males and increased from approximately 25% to approximately 33% in women, among whom AC has long been the most commonly diagnosed histologic type.^{20,23} A similar shift in histology was recently noted in Switzerland by Levi et al., who theorized that “similar exposure to tobacco-related carcinogens leads to similar rates of histologic type-specific lung carcinoma incidence in males and females.”²⁴

In the authors' earlier studies and those of other groups that were performed through the mid-1980s, lower overall lung carcinoma risks were observed for filter smokers and switchers compared with nonfilter cigarette smokers, and in some studies lung carcinoma

risk increased in proportion to the “tar” yield of cigarettes.^{8–13,15} Those earlier reports are consistent with the current findings for SCC, at least in men, because that was the dominant histologic type during that era. The current analysis refines and extends the work of Wynder and Kabat who, a decade ago, characterized the type of cigarette in relation to histologic type of lung tumor. They reported a lower risk of Kreyberg type 1 lung carcinoma (SCC + large cell + oat cell) for filter-only smokers of both genders, but little or no decreased risk for Kreyberg type 2 lung carcinoma (AC + bronchiolar + alveolar cell).¹⁹ Risks were reported for composite histologic categories because the number of LF smokers in each category was relatively small. Small numbers of NF smokers with AC made it necessary to include short term filter (<10 years) smokers with nonfilter smokers in the reference group, which in the current study is composed exclusively of NF smokers. In the current analysis, the percentage of current LF smokers increased from <8% for men and 18% for women in 1977–1980 to 34% of male and 49% of female patients seen in 1991–1995 (Fig. 1).

A strength of this study is that all cases and controls were interviewed in person; no data were obtained from next-of-kin or other surrogates. This is especially important because accurate reports of ciga-

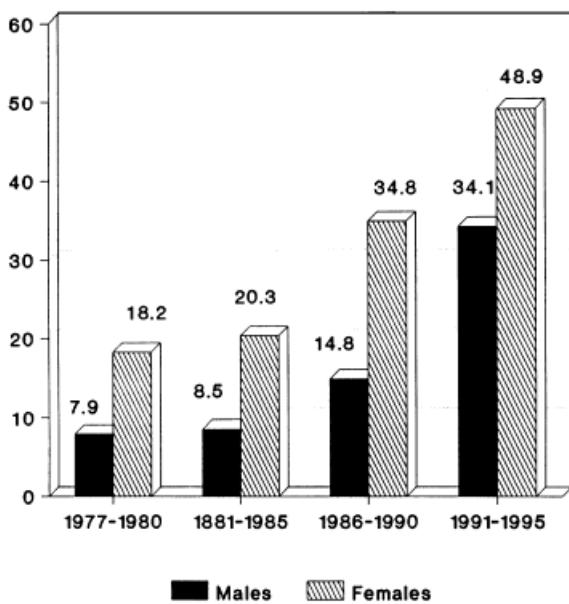


FIGURE 1. Lifetime filter cigarette smokers as a percentage of all current smokers in four time periods by gender. Adapted from American Health Foundation data, 1977–1995.

rette brands and quantity smoked may not always be obtained from relatives. Since 1980, periodic re-interviews with a sample of cases and controls in the authors' study have shown high reliability levels for smoking data.^{25,26} Use of closely supervised, trained interviewers, and rigorous quality control procedures for data management also serve to increase confidence in results. Refusal rates have consistently been <10%, so that little selection bias is believed to exist. Histologies have been taken from final pathologic reports without reconfirmation; however, the study is restricted to the two principal histologic types of lung carcinoma, for which a high degree of interobserver reproducibility has been reported elsewhere.²⁷

A potential limitation in a long term retrospective study such as the current study is that it covers an extended time period (approximately 17 years); the lower mean age of LF smokers compared with current smokers with a history of both nonfilter and filter cigarette usage is a reflection of the fact that younger cohorts of smokers have had more opportunity to be LF smokers.

Such potential time period artifacts are reduced by interviewing controls in the same age strata and time period as the cases, and by adjusting for age in the analyses (which also tends to adjust for duration of smoking). The authors tested the hypotheses that the ORs were homogeneous across 3 time periods (1977–1979, 1980–1985, and 1986–1995); using the method of Breslow and Day²⁸, none of these hypotheses were rejected ($P > 0.05$). Nevertheless, the authors

noted that ORs for AC among female LF smokers and switchers were two to three times higher in the time period 1980–1985 than in either the earlier or later periods, although these estimates were based on very small numbers of female NF smokers.

Using another approach, the authors tabulated the ratio of AC to SCC cases among patients who were diagnosed only during the most recent time period (1991–1995), according to the calendar year in which they began to smoke cigarettes. This revealed a dramatic increase in the AC:SCC ratio in smokers of both genders (shown in Table 4), which was in full support of the authors' hypothesis. Restriction to recently diagnosed cases minimizes the "generational" problem of comparing risks in smokers from different eras and emphasizes the effect of individuals' early cigarette brand choices, because "starter" brands invariably have had higher FTC-rated smoke yields than brands smoked later in life.

LF smoking was associated with a significant reduction of risk for SCC in women; for men the reduction in SCC, although suggestive, was not statistically significant (Table 3). No reduction in AC risk was observed for either men or women. It should be noted that only 8.5% of the male SCC cases interviewed to date were LF smokers; therefore, a definitive test of any effect in males must await further accumulation of cases.

Several factors are likely to have contributed to the lack of any observed decreased risk for AC among current LF smokers. First, the lowering of nicotine yields by as much as 60% (based on machine-smoked, FTC-reported yields for cigarettes³) during the lifetime of these smokers has led to the phenomenon of compensation. This is a behavioral adjustment by those who smoke low yield and medium yield cigarettes (≤ 1.2 mg nicotine). In these cases, the cigarettes are smoked with greater frequency of puff drawing and with greater puff volume, and the smoke is inhaled far more deeply into the lungs^{29–32} to achieve a desired physiologic response to the pharmacologic nicotine. The authors postulate that such a physiologically conditioned change in smoking behavior has led to an altered deposition pattern of particulate matter within the lungs. The particle size distribution in the smoke that is inhaled from filter cigarettes has shifted toward smaller size aerosols with an average greatest dimension of 0.20μ (compared with 0.25μ for the smoke of nonfilter cigarettes³³); it has been estimated that in a long term smoker (≥ 3 years) of high nicotine nonfilter cigarettes the deposition of particles in the upper respiratory tract has its highest density in the bifurcation zone of the tracheobronchial tree.^{34–37} However, on deep inhalation of the smoke, the distribution of smoke particles shifts in such a way that nearly 50%

TABLE 4
Number of Lung Carcinoma Cases with SCC and AC Diagnosed between 1991–1995, and AC:SCC Ratio

Year of onset of cigarette smoking	Males			Females		
	Squamous cell carcinoma	Adenocarcinoma	AC:SCC	Squamous cell carcinoma	Adenocarcinoma	AC:SCC
	No.	No.	Ratio	No.	No.	Ratio
1948 and earlier	41	35	0.85	20	41	2.05
1949–1959	36	50	1.39	27	47	1.74
1960 and later	30	45	1.50	7	49	7.00

SCC: squamous cell carcinoma; AC: adenocarcinoma.

of the particles are trapped in the alveolar regions of the lungs.³⁷ The ratios of SCC to AC along the airways thus correspond roughly to the deposition patterns of smoke particles of different sizes. Furthermore, Yang et al. have noted that the physical distribution of AC parallels the distribution of glandular cells along the surface of the respiratory tract.³⁸

The hypothesis that deeper inhalation by smokers of low yield cigarettes is linked to the upward shift in rates of AC relative to SCC also agrees with the observation that lung neoplasms in primary smokers of pipes and cigars, whose smoke inhalation is shallow, are usually SCC arising from the major bronchi.³⁹ Cigars and pipes generate alkaline smoke with significant amounts of unprotonated (free) nicotine that is rapidly absorbed through the oral mucosa, thus quickly satisfying nicotine demand without deep inhalation,⁴⁰ so that the smokers inhale little or no smoke from these products.

A second, complementary hypothesis suggests that smoking cigarettes with lower “tar” yields may not reduce one’s risk for AC because some of the potential benefit of the lower levels of polynuclear aromatic hydrocarbons (PAH) in the smoke of these cigarettes is offset by the higher levels of organ specific, carcinogenic tobacco specific nitrosamines (TSNAs) in the smoke of modern day cigarettes.⁴¹ Within the past two decades, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) yield, used as a surrogate measure for total TSNA and whose metabolites can be detected in the urine of smokers,⁴² increased by nearly 75% from 110 ng per cigarette in 1978 to 191 ng in 1995 in the smoke of U.S. nonfilter cigarettes; similar trends for NNK were observed in the smoke of other cigarettes, including filter cigarettes. By contrast, the per-cigarette emission of benzo(a)pyrene (BaP) (a surrogate measure for levels of carcinogenic PAH) in the smoke of the best-selling U.S. nonfilter cigarette declined from 52 ng in 1965 to 18 ng in 1995.⁴³ The authors believe it to be significant, in keeping with differences in histologic types of human lung carcinoma,

that NNK induces primarily adenoma and AC of the lung in mice, rats, and Syrian golden hamsters, independent of site of application,⁴⁴ whereas intratracheal instillation of BaP and other carcinogenic PAH preferentially induces SCC in rats and hamsters.⁴⁵ Workers exposed to aerosols from combustion products with high concentrations of carcinogenic PAH present mainly with SCC.^{46,47} Thus, changes in the population ratio of SCC to AC are consistent with changes in the concentrations of histology specific lung carcinogens in cigarette smoke.

As the number of persons who have smoked low yield cigarettes (e.g., < 10 mg “tar,” < 1.0 mg nicotine) for their lifetime continues to grow, and as more of these smokers who exceed the latency associated with smoking such cigarettes develop lung carcinoma, opportunities for evaluating and quantifying the health risks of these newer tobacco products will also increase. Such studies need to be performed on a broad basis because tobacco use continues to be the major cause of preventable cancer mortality in the U.S.

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