

## Risk Factors for Lung Cancer in Young Adults

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Risk factors for early onset of lung cancer are relatively unknown. In a case-control study, carried out in Germany between 1990 and 1996, the effects of smoking and familial aggregation of cancer were compared in 251 young cases and 280 young controls ( $\leq 45$  years) and in 2,009 older cases and 2,039 older controls (55–69 years). The male/female ratio was 2.6/1 in young patients and 5.6/1 in older patients. Adenocarcinomas were more frequent in young men than in older men (41% vs. 28%). Duration of smoking and amount smoked showed significantly increased odds ratios for lung cancer in both age groups. Lung cancer in a first degree relative was associated with a 2.6-fold (95% confidence interval (CI) 1.1–6.0) increase in the risk of lung cancer in the young age group, but no elevated risk was seen in the older group (OR = 1.2, 95% CI 0.9–1.6). Smoking-related cancer in relatives with the age at diagnosis under 46 years was associated with an increased risk of lung cancer in the young group (OR = 5.6, 95% CI 0.7–46.9) but not in the older group (OR = 0.7, 95% CI 0.3–1.5). Results indicated that lung cancer risk in young and older age groups shows remarkable differences with respect to sex, histologic type, and genetic predisposition. *Am J Epidemiol* 1998;147: 1028–37.

adult; case-control studies; family; lung neoplasms; smoking

Lung cancer is the most common fatal malignancy among men in the western world and, since 1986, this has also been true of women in the United States. In Germany, lung cancer is still the fourth most common malignant tumor in women, but there has been a dramatic increase in bronchogenic carcinoma among women in the last two decades. Incidence is highest between the ages of 60 and 70, with only about 3 percent of cases occurring in patients aged 45 years or less. The majority of studies that have specifically dealt with younger people have involved relatively few patients and were mainly concerned with surgical treatment or survival rates (1–5). Risk factors that contribute to an early onset of lung cancer are therefore still relatively unknown.

Several case-control studies of young subjects have found a high proportion of female patients, a predominance of adenocarcinoma, and an association between lung cancer and smoking (6–8). Other studies (2, 9), which compared old and young cases without controls,

have found more and heavier smokers in the younger age groups. Results of segregation analyses (10) indicate that the inheritance of a rare major autosomal gene results in an earlier age of onset of lung cancer. Our aim was to identify factors that might contribute to the early onset of lung cancer. We have therefore compared the effects of smoking and familial cancer in a young case-control study and in an older case-control study.

### MATERIALS AND METHODS

#### Study design

Data for both age groups were derived from a case-control study of lung cancer risk and indoor radon conducted between 1990 and 1996 in several regions of East and West Germany (11). A total of around 4,000 cases and 4,000 population controls were interviewed by trained interviewers. Histologically or cytologically confirmed lung cancer cases with primary tumors were recruited from 15 study clinics. Cases were eligible if the following conditions were met: 1) they were aged less than 75; 2) they were resident in the study region; 3) they had lived in Germany for more than 25 years; 4) the interviews could be conducted within 3 months of diagnosis; and 5) they were not too ill. The response rate among eligible cases was 76 percent. A reference pathologist reviewed about 75

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Abbreviations: CI, confidence interval; OR, odds ratio.

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percent of the pathologic material. Population controls satisfying inclusion criteria 1–3 were randomly selected from mandatory registries or by modified random digit dialing and were frequency matched to cases on sex, age, and region. The response rate for controls was 41 percent. In a subsample of refusals, a nonresponse analysis was conducted. Nonresponse was mainly due to refusal of long-term measurements of radon (1 year) required in the subjects' homes (38 percent), no time for interview and organization of measurement (13 percent), followed by illness (13 percent) and other reasons.

A standardized questionnaire was used to determine basic demographic characteristics in addition to details on active smoking history, occupational history, and familial diseases. Subjects were defined as young if they were aged 45 years or less, in accordance with other studies (1, 5, 12). For comparison, subjects aged 55–69 years were defined as old. Subjects aged between 46 and 54 years were excluded to clearly separate the two age groups, and those over 69 years were excluded because their recollection of past exposures might be less accurate than that of the younger age groups. Cases and controls in both age groups were frequency matched by age (<41, 41–45, 55–59, 60–64, 65–69 years), region (four centers), and sex.

To avoid misclassification due to different pathologists, diagnoses of tumor histology from the reference pathologist were used where available, with missing reference histology replaced by diagnoses from the clinic pathologist. The category "other" includes a few "large cell carcinomas," mixed types, and material for which no classification was possible.

### Definitions

Subjects were defined as smokers if they had ever smoked regularly (at least one cigarette per day, four cigarillos/week, three cigars, or three pipes/week) for at least 6 months. Smoking exposure was explored in a series of phases, where a new phase was defined as a change in amount or type of tobacco product smoked. In each phase, information was available on the type of tobacco, amount smoked, duration in years, times of cessation, and year of starting. The average number of cigarettes smoked per day was then calculated as the time-weighted average over all smoking phases. Smokers who had only used products other than cigarettes were excluded from these calculations.

Data were also collected on lifetime occupational history. Subjects who reported a job with a potential lung cancer risk were asked in more detail about working conditions and especially about exposure to asbestos. Asbestos exposure was classified as a binary variable without taking duration or intensity of expo-

sure into account.

Information on history of cancer among first degree relatives (parents and siblings) was gathered, including age at disease, site of cancer, and relation to the subject. These data could not be validated by death certificate, and information on the smoking habits of relatives was not obtained. Subjects were defined as having cancer in the family if at least one relative with cancer was reported. This factor was defined for lung cancer, cancer of any site, and smoking-related cancers (cancer of lung, bladder, mouth, esophagus, liver, pancreas, larynx, uterus, or cervix). Subjects who didn't know whether their parents were still alive were excluded from analyses of this factor.

### Statistical methods

Differences between groups were assessed using chi-square tests for independence of categorical variables and *t* tests for continuous variables. Risk analyses used unconditional logistic regression using the SAS procedure LOGISTIC (13), and all models included the matching variables age, region, and sex.

The effects of smoking were examined in terms of smoking status, average number of cigarettes per day, duration of smoking, and pack-years. The analysis for average number of cigarettes smoked was repeated with attention restricted to the time window 5–15 years prior to interview. This time period may be the most relevant for carcinogenesis and reduces the problem of changes in amount smoked over time. Analyses of the effects of smoking were all adjusted for asbestos exposure.

The effects of family history were additionally adjusted for potential unequal pedigree size, by including the number of siblings, and the possible confounding effects of smoking and asbestos exposure. Smoking was included by fitting pack-years as a continuous variable ( $\log(\text{pack-year} + 1)$ ) and tobacco product as a binary variable (cigarettes vs. other products only). Differences in odds for subjects with a family history of cancer between the old and young age groups were formally tested by including an appropriate interaction term in the logistic model. To investigate whether there was an aggregation of early onset of cancer in the family, analyses were repeated, restricting attention to relatives with disease at age 45 years or less.

Radon was not considered as a particular risk factor in this study, because it is a weak risk factor. To detect a risk, big sample sizes and high prevalence of indoor radon are needed. Both are not given in this small subgroup of young persons. It could also be shown that radon is not a confounder. Additional adjustment of lung cancer risk from smoking or familial cancer by radon didn't change the results and was not presented.

## RESULTS

A total of 251 cases and 280 controls were included in the young age group (table 1), while the older group consisted of 2,009 cases and 2,039 controls. The male/female ratio in the young group was 2.6/1 compared with 5.6/1 in the older group. The mean age was 40 years in the young and 62 years in the older group. The youngest female case was 27 years, and the youngest male case 28 years.

The most common tumor type among women was adenocarcinoma (table 1), and there was no statistical difference in tumor histology between old and young patients (chi-square test, 3 df,  $p = 0.3$ ). When attention was restricted to smokers only, the proportions in young women were 46.8 percent adenocarcinoma, 32.3 percent small cell carcinoma, 14.5 percent squamous carcinoma, and 6.4 percent other types compared with 38.1, 27.8, 24.9, and 9.3 percent, respectively, in the older group. The most common tumor type among young men was adenocarcinoma (41.0 percent), followed by 24.0 percent small cell carcinoma, 26.2 percent squamous carcinoma, and 8.7 percent other types. Conversely, the most common type in older men was squamous carcinoma (42.1 percent) followed by 28.0 percent adenocarcinoma, 22.5 percent small cell carcinoma, and 7.5 percent other, and this difference between the two age groups was statistically significant (chi-square test, 3 df,  $p = 0.001$ ). The two distributions were the same when attention was restricted to smokers only.

The proportions of lifelong nonsmokers, exsmokers, current smokers of cigarettes or mixed tobacco products, and current smokers of tobacco products other than cigarettes only are given in table 1. Among female cases, more older women (32 percent) were lifelong nonsmokers compared with young women (9 percent). The same was true of female controls, with 64 percent nonsmokers in the older and 48 percent in the younger group. In contrast, the differences in male cases and controls were very small. Three percent of young cases were nonsmokers compared with 1 percent of the older group, and 27 percent of young controls didn't smoke compared with 23 percent of older controls. The percentage of exsmokers was generally higher in the older age groups.

Characteristics of smoking habits for both age groups are shown in table 2. Young male cases and controls started smoking 2 years earlier on average than the older group, and the difference was even more marked in women with the younger group starting around 5 years earlier than the older group. There was only a slight difference in age started smoking between young men and women. Young male controls began at an average age of 17.9 years, while young

female controls started at an average age of 18.5 years. The younger group generally smoked more cigarettes per day than the older group, and women tended to smoke fewer cigarettes than men. Young male controls smoked an average of 18 cigarettes per day compared with 13 for older controls, and young and older female controls smoked an average of 16 and 11 cigarettes per day, respectively. As one would expect, there was a difference of about 15 years in the average duration of smoking between the older and younger age groups. Odds ratios for the effect of smoking are shown in table 3. The odds ratio for current smokers compared with never smokers was substantially higher in older men (odds ratio (OR) = 41.9, 95 percent confidence interval (CI) 27.1–64.6) than in young men (OR = 15.9, 95 percent CI 6.5–38.5). Conversely, there were much higher odds ratios in young women (OR = 29.9, 95 percent CI 9.5–94.6) compared with older women (OR = 6.4, 95 percent CI 4.2–9.6). The pattern of odds ratios for average number of cigarettes smoked per day indicated that older men had much higher odds ratios than young men, while older women had lower odds ratios than young women. When the analysis was repeated for the period 5–15 years prior to the interview, the patterns were the same. Similar results were seen in the analyses of duration of smoking and pack-years.

A family history of lung cancer was reported by 10 percent of young lung cancer cases as compared with 3 percent of young controls (table 4) with an odds ratio of 3.3 (95 percent CI 1.5–7.3). Adjusting for smoking, exposure to asbestos and number of siblings gave an odds ratio of 2.6 (95 percent CI 1.1–6.0). In contrast, family history of lung cancer did not appear to contribute to lung cancer risk in the older age group (OR = 1.2, 95 percent CI 0.9–1.6). A test for interaction was close to statistical significance ( $p = 0.058$ ), indicating a difference in the odds ratios for family history between the age groups. When the age of the relative with lung cancer was considered, six (25 percent) of the 24 young cases with a family history had a relative aged 45 years or less at the onset of disease compared with less than 5 percent in the older cases and controls.

Similar analyses were carried out for a family history of smoking-related cancer, and there was no evidence of an increase in odds in either age group. When attention was restricted to the impact of having a relative with disease at age 45 years or less, there was a significantly raised odds ratio of 12.2 (95 percent CI 1.5–93.2) in the younger group. After additional adjustment, this odds ratio was reduced to a fivefold increase (OR = 5.6, 95 percent CI 0.7–46.9). The difference in odds ratios between the age groups

TABLE 1. Characteristics of both age groups by sex and case-control status, Germany, 1990–1996

	No.	Age (years)			Marital status (%)				Education by years of school (%)				
		Mean	Median	Minimum	Single	Married	Widowed	Divorced	<9	9	10–12	>12	Other
Age ≤45 years													
Male													
Cases	183	40.2	41	28	13.1	74.9	0	12.0	1.6	65.6	24.6	7.1	1.1
Controls	200	40.0	41	26	8.5	84.5	0	7.0	0	36.0	40.0	23.0	1.0
Female													
Cases	68	40.4	42	27	2.9	80.9	1.5	14.7	2.9	73.5	14.7	5.9	2.9
Controls	80	40.6	42	24	7.5	77.6	2.5	12.5	0	42.5	37.3	18.8	1.3
Age 55–69 years													
Male													
Cases	1,709	62.3	63	55	2.4	89.7	5.0	2.8	2.3	82.2	9.6	5.2	0.8
Controls	1,761	62.2	62	55	2.1	92.0	3.8	2.0	1.3	70.0	15.8	15.0	1.0
Female													
Cases	300	62.0	62	55	5.3	64.0	22.3	8.3	2.0	80.0	14.1	3.3	1.0
Controls	278	62.0	62	55	6.8	64.2	23.0	5.8	2.2	63.0	20.9	12.6	1.4
Tumor type (%)													
Smoking status (%)													
		Small cell	Squamous	Adenocarcinoma	Other*	Lifelong nonsmoker†	Exsmoker‡	Current cigarette smoker§	Current other smoker¶				
Age ≤45 years													
Male													
Cases		24.0		41.0	8.7	3.3	4.9	91.8	0.0				
Controls			26.2			27.0	23.5	46.5	3.0				
Female													
Cases		30.9		44.1	8.8	8.8	10.3	80.9	0.0				
Controls			16.2			47.5	23.8	27.5	1.3				
Age 55–69 years													
Male													
Cases		22.5		28.0	7.5	1.3	25.4	71.7	1.5				
Controls			42.1			22.9	47.4	28.9	0.9				
Female													
Cases		20.3		47.0	10.0	31.7	11.7	55.7	1.0				
Controls			22.7			63.7	16.9	19.4	0.0				

\* Large cell carcinoma, mixed types, and no classification possible.

† Never smoked more than one cigarette per day regularly for longer than 6 months.

‡ Quit smoking more than 5 years prior to interview.

§ Ever smoked cigarettes within 5 years of interview.

¶ Smoked only cigars, pipes, or cigarillos within 5 years of interview.

TABLE 2. Quantitative characteristics of cigarette smoking in both age groups, by sex, among cigarette smokers only,\* Germany, 1990-1996

	No.		Age started smoking (years)				Average daily amount (cigarettes/day)				Duration of smoking (years)				Pack-years (no.)				
	Male	Female	Male		Female		Male		Female		Male		Female		Male		Female		
			Mean	SD†	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Age <45 years																			
Cases	177	62	16.7	2.4	17.4	3.9	22.8	9.3	19.2	12.0	22.9	4.5	20.9	6.5	26.7	13.2	21.6	17.3	
Controls	139	41	17.9	3.3	18.5	3.5	18.0	8.7	15.7	10.5	17.1	7.4	14.9	7.6	16.4	12.1	10.9	9.2	
Age 55-69 years																			
Cases	1,654	202	18.9	3.9	22.5	7.0	19.5	9.2	15.2	8.5	37.3	10.2	35.5	10.9	37.1	20.3	28.5	17.8	
Controls	1,315	101	19.4	5.0	24.5	8.0	12.8	7.3	11.2	8.1	27.4	13.3	26.0	13.6	23.1	19.9	16.7	17.2	

\* Ever smoked cigarettes (includes smokers of mixed tobacco products).

† SD, standard deviation.

was close to statistical significance ( $p = 0.056$ ). The numbers of relatives with lung cancer and smoking-related cancer and their relation with the subjects are presented in table 5.

Odds ratios for lung cancer by age group, family history, and smoking status are given in table 6. Young never smokers had a twofold increase in odds associated with a family history of lung cancer, and this increase was even more marked in those who had ever smoked (OR = 16.6 vs. 5.7). However, a formal test of interaction between smoking status and family history of lung cancer was not significant in either the young or the older age group.

## DISCUSSION

The predominance of adenocarcinoma among young patients is similar to that seen in most published series (1-4, 6, 9, 14-16). Although the etiologic and pathogenetic bases of the different types of lung cancer remain uncertain, a recent trend of increasing adenocarcinoma has been documented in many regions around the world (17-21). These changes in histologic patterns have been interpreted as possibly signaling changes in causal factors (22, 23) in addition to changes in classification. Since most of the pathologic material was reviewed by one pathologist without knowledge of the patients' age, the classification effect can be neglected. Studies of the last three decades consistently report a predominance of adenocarcinoma in young compared with older patients. This cannot be explained by general trends alone and indicates the presence of other possible etiologic factors in young cases compared with older ones.

Cigarette smoking has been identified as the major cause of lung cancer (24), with risk directly related to the number of cigarettes smoked per day, the duration of smoking, the age of starting smoking, and pack-years. Of the young male and young female patients in this study, 97 percent and 91 percent, respectively, reported smoking at some time. In other series on young subjects, the range has been between 80 and 95 percent (1-4, 12, 15, 25). There are only a few studies dealing with smoking risk in younger patients, but all have showed an increased relative risk estimate for lung cancer among smokers compared with nonsmokers and a significant dose-response effect with amount smoked (6-8).

The question of whether particular smoking patterns lead to an early onset of lung cancer is still open. Wynder and Graham (26) found that younger patients who developed lung cancer smoked more than older patients. They concluded that the greater the intake, the earlier cancer would develop in a susceptible pa-

**TABLE 3. Odds ratios for different smoking variables by age group and sex, Germany, 1990–1996**

	Age ≤45 years				Age 55–69 years			
	Male		Female		Male		Female	
	OR*	95% CI*	OR	95% CI	OR	95% CI	OR	95% CI
<b>Smoking status</b>								
Never smoker	1.0		1.0		1.0		1.0	
Exsmoker†	1.7	0.6–5.2	2.5	0.7–9.0	9.1	5.9–14.1	1.4	0.8–2.4
Current smoker‡	15.9	6.5–38.5	29.9	9.5–94.6	41.9	27.1–64.6	6.4	4.2–9.6
<b>Average no. of cigarettes/day</b>								
Never smoker	1.0		1.0		1.0		1.0	
≤9	2.5	0.7–8.2	5.7	1.6–16.6	8.2	5.2–13.0	2.0	1.2–3.3
10–19	8.7	3.5–21.9	11.8	3.5–29.0	25.1	16.2–38.7	5.4	3.5–8.6
20–29	19.5	7.5–50.3	12.1	3.0–48.0	32.8	20.9–51.4	7.7	3.5–17.3
≥30	20.8	7.2–60.5			33.3	20.5–54.0		
<b>Average no. of cigarettes/day 5–15 years before interview</b>								
Never smoker	1.0		1.0		1.0		1.0	
≤9	3.6	0.9–14.1	5.4	1.3–22.3	10.9	6.6–18.0	2.9	1.4–5.7
10–19	8.8	3.4–23.0	20.6	5.9–71.1	26.5	17.1–41.4	6.2	3.5–11.1
20–29	13.7	5.4–34.6	16.8	4.7–59.7	39.5	25.7–60.9	7.8	4.4–13.8
≥30	32.1	11.5–89.7	71.2	10.8–469	50.1	31.8–79.1	9.7	3.7–25.1
<b>Duration of smoking (years)</b>								
Never smoker	1.0		1.0		1.0		1.0	
≤19	4.0	1.6–10.2	4.9	1.7–14.2	4.9	3.1–7.9	0.9	0.5–1.6
20–39	26.3	10.3–66.8	47.5	13.2–173	20.9	13.5–32.2	4.9	3.1–7.6
≥40					54.5	34.9–85.2	8.3	4.7–14.5
<b>Pack-years</b>								
Never smoker	1.0		1.0		1.0		1.0	
≤19	5.2	2.1–13.1	7.2	2.6–19.8	8.5	5.5–13.2	1.7	1.1–2.6
20–39	27.6	10.7–71.5	31.5	7.8–126	30.1	19.4–46.7	9.8	5.5–17.2
≥40	33.5	9.8–114.1			53.6	34.1–84.2	11.9	5.4–25.8

\* OR, odds ratio adjusted for age, region, and exposure to asbestos; CI, confidence interval.

† Quit smoking at least 5 years prior to interview.

‡ Current smoker of cigarettes (includes smokers of mixed tobacco products).

**TABLE 4. Odds ratios for history of cancer in at least one first degree relative (parents or siblings) and in at least one first degree relative (parents or siblings) with age at onset less than 46 years for both age groups, Germany, 1990–1996\***

Cancer site	Age ≤45 years				Age 55–69 years				Test for interaction between age group and family history (p value)
	History of cancer in family		OR†,‡	95% CI†	History of cancer in family		OR§	95% CI	
	Case (n = 242)	Control (n = 276)			Case (n = 1,984)	Control (n = 2,026)			
Lung cancer/all ages	24	9	3.3	1.1–6.0	139	106	1.4	0.9–1.6	0.058
Lung cancer/≤45¶	6				5	6	0.8	0.2–2.4	
Smoking-related cancer#/all ages	37	22	2.1	0.9–3.3	261	255	1.0	0.7–1.1	0.067
Smoking related cancer/≤45	10	1	12.2	0.7–46.9	16	18	0.9	0.3–1.5	
Cancer at any site/all ages	81	77	1.3	0.8–1.9	705	736	1.0	0.8–1.1	0.292
Cancer at any site/≤45	23	11	2.6	0.8–4.4	65	79	0.8	0.5–1.0	

\* Subjects without knowledge of the vital status of their parents were excluded.

† OR, odds ratio; CI, confidence interval.

‡ Odds ratio adjusted for age, sex, and region.

§ Odds ratio adjusted for age, sex, region, asbestos, pack-years, tobacco type, and number of siblings.

¶ Age at disease of relative less than 46 years.

# Lung, bladder, mouth, esophagus, liver, pancreas, larynx, uterine, cervix.

tient. Passey (27), however, found that the age of onset of cancer was not related to the amount smoked nor the age at which smoking began.

We observed a higher number of cigarettes smoked per day in young subjects compared with older subjects, independently of case-control status, and this may be due to the change in nicotine content and filter usage over the last two decades. Since the 1960s, the nicotine content weighted by share of market has decreased in cigarettes in the former Federal Republic of Germany from 1.14 to 0.78 mg (28). Studies in the United States (29) and Germany (28) show that smokers compensate for lower nicotine content by smoking an increased amount. Another explanation could be one of deeper inhalation. In fact, differences in the amount smoked, duration, filter usage, nicotine contents, number of exsmokers, inhalation, and age at starting smoking in the two birth cohorts don't allow a direct comparison of smoking risk between the two age groups.

Considering the older age group alone, there were substantial differences in the smoking patterns of women and men. Odds ratios for smoking among women were much lower than among men, and there were many more adenocarcinomas in women. Conversely, young women showed a similar smoking pattern, a similar lung cancer risk due to smoking, and a similar tumor type distribution to those of young men. Studies in the United States show that the smoking pattern of females has converged toward that of males in younger cohorts (24) and that the changes in smoking practices among females have been accompanied by concurrent changes in lung cancer risk patterns.

Many epidemiologic and clinical studies have indicated familial aggregation of lung cancer (30–37). Our findings demonstrated a threefold increase in risk of lung cancer in subjects younger than 46 years if relatives were also affected by lung cancer and no elevated risk in older people. The validity of reported illness of relatives must be considered in interpreting these results. The information was obtained by interview and could not be compared with other sources. This technique might introduce either random or systematic error in the classification of the participants due to overreporting by cases. Such bias may be present in the older group, but in this case there would be an overestimation of risk. For individuals aged 40 years on average, it seems unlikely that a death from lung cancer in a parent or sibling would not be remembered. This is supported by the fact that no big differences were found when the number of fathers reported by controls as having lung cancer was compared with mortality data for lung cancer in men in Germany (38).

**TABLE 5. Number and type of relative with lung cancer or smoking-related cancer by age at disease (all ages,  $\leq 45$  years), age group, and case-control status, Germany, 1990–1996**

	Age $\leq 45$ years		Age 55–69 years	
	Case (n = 242)	Control (n = 276)	Case (n = 1,984)	Control (n = 2,026)
Subjects with at least one relative with lung cancer	24 (6)*	9 (0)	139 (5)	106 (6)
All relatives with lung cancer	24 (6)	9 (0)	144 (5)	108 (6)
Father	20 (3)	8 (0)	86 (1)	68 (1)
Mother	1 (0)	1 (0)	15 (0)	18 (2)
Brother	1 (1)	0 (0)	36 (3)	16 (3)
Sister	2 (2)	0 (0)	7 (1)	6 (0)
Subjects with at least one relative with smoking-related cancer†	37 (10)	22 (1)	261 (16)	255 (18)
All relatives with smoking-related cancer	41 (10)	25 (1)	283 (16)	270 (18)
Father	30 (4)	20 (1)	144 (3)	141 (4)
Mother	7 (2)	5 (0)	62 (0)	68 (4)
Brother	2 (2)	0 (0)	60 (8)	42 (8)
Sister	2 (2)	0 (0)	17 (5)	19 (2)

\* Numbers in parentheses, number of relatives with age at disease less than 46 years.

† Lung, bladder, mouth, esophagus, liver, pancreas, larynx, uterine, cervix.

**TABLE 6. Odds ratios for lung cancer by smoking status and family history of lung cancer for both age groups (reference category is nonsmokers with no positive history of cancer in family), Germany, 1990–1996**

Smoking status	No positive family history of lung cancer				Positive family history of lung cancer			
	Case	Control	OR*,†	95% CI*	Case	Control	OR†	95% CI
Age $\leq 45$ years								
Nonsmoker	11	88	1.0		1	2	2.3	0.2–26.6
Ever smoker	207	179	5.7	3.3–9.8	23	7	16.6	6.1–45.0
Age 55–69 years								
Nonsmoker	108	548	1.0		7	30	0.9	0.4–2.2
Ever smoker	1,737	1,372	7.3	5.9–9.2	132	76	9.3	6.5–13.3

\* OR, odds ratio; CI, confidence interval.

† Odds ratio adjusted for age, sex, region, and exposure to asbestos.

Bondy et al. (39) recently examined the validity of patient reports of a family history of cancer by validating them using medical records. In this study, subjects correctly identified the primary site of cancer for 88 percent of cases in first degree relatives and for lung cancer in 85 percent.

A limitation of the present study is the use of a case-control approach in the analysis of family history. It has been shown that, even without case-control differences in the number or ages of relatives, positive family history tends to overestimate relative risk measures in individual relatives (40). A second limitation is that no information was available concerning the smoking habits of relatives. Therefore, it was not possible to determine how much of the familial aggregation of lung cancers was due to shared environments of family members. Smoking, occupation, and diet are possible risk factors that cluster in families and ac-

count for some of the observed aggregation. However, a possible genetic component, especially in young cases, is supported by the finding of familial risk of lung cancer only in the young group and the familial aggregation of early onset lung cancer in young cases. Moreover, two recent published studies (10, 41) concerning the age of onset of lung cancer and familial aggregation show results that are consistent with our findings. Both used a cohort approach, and information on risk factors for lung cancer in relatives was available.

Sellers et al. (10, 42) and Bailey-Wilson et al. (43) have carried out segregation analyses that allow for variable age of onset of lung cancer and smoking history. Results indicated compatibility of the data with Mendelian codominant inheritance of a rare major autosomal gene that produces earlier age of onset of cancer. Segregation at this putative locus could



account for 69 percent and 47 percent of the cumulative incidence of lung cancer in individuals up to ages 50 and 60 years, respectively. The gene was involved in only 22 percent of all lung cancers in persons up to age 70. Schwartz et al. (41) analyzed familial risk of lung cancer in a case-control study of nonsmokers with 257 cases and 277 controls and their relatives. She found a 7.2-fold increase in risk for lung cancer in a first degree relative in the young age group (40–59 years). This significant increase in risk remained after adjustment for the smoking, occupational, and medical history of each family member (relative risk = 6.1, 95 percent CI 1.1–33.4). In older subjects, a positive family history of lung cancer did not increase lung cancer risk.

In conclusion, smoking is the main risk factor for young and older lung cancer cases. Adenocarcinoma was more frequent in young male patients than in older men. A familial aggregation of lung cancer, which increased the lung cancer risk by a factor of three, was seen only in the younger age group. We conclude that genetic predisposition in combination with the main risk factor, smoking, could play a role in an earlier age of onset. This should be examined by future molecular genetic studies.

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