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Environmental Tobacco Smoke and Lung Cancer: A Case-Control Study in Germany

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To assess the association between exposure to environmental tobacco smoke (ETS) and lung cancer, the authors personally interviewed 292 lifelong nonsmoking lung cancer cases (recruited from 15 hospitals in the study area) and 1,338 nonsmoking controls (randomly selected by population registries) between 1990 and 1996 in Germany. Subjects were asked by a standardized questionnaire about exposure to ETS in childhood, by spouse, at work, and in transportation and social settings. Several indicators of these different sources of exposure were investigated, using not or low exposed subjects as the reference category. The most informative quantification index was weighted duration of exposure (hours × level of smokiness). No effect of ETS exposure during childhood and no clear effect of spousal ETS were observed. However, for the highest category of exposure, clear effects of ETS at the workplace (odds ratio (OR) = 1.93; 95% confidence interval (CI): 1.04, 3.58), in vehicles (OR = 2.64; 95% CI: 1.30, 5.36), and from all sources combined (OR = 1.39; 95% CI: 0.96, 2.01) were found. Adjustment for occupational carcinogens, radon, and diet did not appreciably change the results. These findings suggest that exposures to high levels of ETS at the workplace and in other public indoor settings appear to be important risk factors for lung cancer risk in nonsmokers. *Am J Epidemiol* 2000;151:241–50.

case-control studies; lung neoplasms; tobacco smoke pollution

Since 1981, over 40 epidemiologic studies have examined the relation between exposure to environmental tobacco smoke (ETS) and lung cancer in lifetime nonsmokers. The studies provided inconsistent results. A significantly increased lung cancer risk associated with ETS exposure, however, was found after summarizing and evaluating these studies (1, 2). In 1992, the US Environmental Protection Agency (3) and later the California Environmental Protection Agency (4) concluded that ETS is a human carcinogen, as did the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (5, 6). However, criticisms were raised that the weak association of ETS and lung cancer is likely to be affected by confounding and other sources of bias, such as misclassification of smoking status, recall bias, diagnostic bias, and especially heterogeneity in meta-analyses (7, 8). Moreover, most of these studies considered ETS exposure from the spouse only and not from other sources such as ETS at the workplace, during transportation, or in social settings.

Since relatively few studies of ETS exposure are available from Europe (9–16), the International Agency for Research on Cancer has coordinated and recently published the results of a multicenter case-control study of lung cancer in nonsmokers (17). Twelve centers from seven European countries participated in this study, including overall 650 cases and 1,542 controls. ETS exposure during childhood was not associated with an increased risk for lung cancer (odds ratio (OR) = 0.78; 95 percent confidence interval (CI): 0.64, 0.96). The odds ratio for ever exposure to spouse was 1.16 (95 percent CI: 0.93, 1.44), demonstrating no clear dose-response relation with cumulative spousal ETS exposure. The odds ratio for ever exposure to workplace ETS was 1.17 (95 percent CI: 0.94, 1.45), with some evidence of increasing risk for increasing duration of exposure. A subset of 173 cases and 215 controls from a German case-control study of lung cancer and residential radon (18, 19) had been included in the multicenter

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Abbreviations: CI, confidence interval; ETS, environmental tobacco smoke; OR, odds ratio.

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study from the International Agency for Research on Cancer. Since then, information on an additional 119 nonsmoking cases and 1,123 nonsmoking controls from this ongoing German study has become available. Together, this large sample size allows us to further investigate in detail different sources of ETS exposure in the German study population.

MATERIALS AND METHODS

Study design

Data on nonsmokers 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 (18). A total of 4,303 cases and 4,451 population controls were personally interviewed by regularly trained interviewers. Newly diagnosed cases with histologically or cytologically confirmed lung cancer as a primary tumor were recruited from 15 study clinics in the defined study area. Cases were eligible, if 1) they were younger than 75 years, 2) they were currently resident in the study region, 3) they lived longer than 25 years in Germany, 4) the interviews were within 3 months after diagnosis, and 5) they were not too ill. The response rate of eligible cases was 76 percent. A reference pathologist reviewed about 75 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 the cases on sex, age (in 5-year classes), and region. The response rate of eligible controls was 41 percent.

A standardized questionnaire was used to ascertain basic demographic characteristics as well as details on residential history, active and passive smoking history, dietary habits, and occupational and medical history. Subjects who ever smoked at least one cigarette/day, four cigarillos/week, three cigars/week, or three pipes/week for longer than 6 months were classified as smokers, and their lifetime smoking history was collected. All other subjects were defined as nonsmokers, and information on a history of ETS exposure was gathered. Nonsmokers who did not fulfill the criteria for smokers but who smoked at some time in their lives (e.g., special events) were asked additional questions for a detailed history of occasional smoking. Only those subjects who reported that they had not smoked more than 400 cigarettes during their life were eligible for this study.

Assessment and quantification of exposure to ETS

The questionnaire on ETS gathered information about ETS exposure during childhood, during adulthood at home (spouse or other cohabitants), at the workplace, in vehicles, and at other public places (e.g., in restaurants). It had been developed on the basis of the results of a study on urinary cotinine levels and ETS exposure (20) and was also used in the multicenter European study. To investigate lung cancer risk by ETS, we calculated either binary (ever/never exposure) or quantitative variables of ETS exposure for all sources of exposure.

We used as quantitative variable of childhood ETS exposure (up to age 18) the cumulative numbers of hours of exposure, denoted as duration in hours, where hours per year were defined in one of the following ways: several hours/day = 1,000 hours/year; daily, only a short while = 300 hours/year; 2–4 times/week = 300 hours/year; approximately once a week = 100 hours/year; rarely = 25 hours/year; and never = 0. Quantitative variables of exposure to ETS from the spouse as well as from other cohabitants included 1) the cumulative number of hours of exposure, denoted as duration in hours, and 2) the cumulative exposure expressed as pack-years, which was defined as the product of the number of years of the exposure and the average number of cigarettes smoked per day from the spouse in the presence of the index subject. Exposure from the workplace was defined as 1) duration of exposure in hours and 2) duration of exposure in cumulative hours weighted for a subjective index of smokiness (in hours × smokiness, where smokiness was defined as 1 = not visible but smellable, 2 = visible, 3 = very smoky). Pack-years were not calculated, since no information about the number of cigarettes smoked at the workplace in the presence of the subject was available. ETS exposure from other public places (bars, restaurants, or vehicles) was derived in terms of duration of exposure in hours weighted for the level of smokiness.

We calculated the 75th and 90th percentiles for all nonzero values of cases and controls from each source of exposure. Subjects who were never exposed or whose exposure was below the third quartile comprised the reference category in all analyses with quantitative variables. The choice of this cutpoint is based on the experience from a urinary cotinine study conducted in Poland and Germany (21), which showed a smaller degree of misclassification in the highest quartile compared with the three lowest quartiles of distribution.

Summary indicators for duration of exposure (in cumulative hours × level of smokiness) from all sources of ETS together were derived in the following way. Individuals were considered to be not exposed or as having low exposure from different sources, if the exposure to any source was below the third quartile of the distribution among cases and controls. If their exposure was above the third quartile for any source

and below the 90 percent centile for all sources, their exposure was considered to be medium. Exposure above the 90 percent centile for any source was defined as high.

Potential confounding factors such as occupation, radon exposure, diet, family history of lung cancer, previous nonmalignant lung disease, and social class were quantified as follows. Subjects were classified as having been occupationally exposed to known or suspected lung carcinogens if they had worked for at least 6 months in a job entailing exposure to recognized or suspected lung carcinogens (22, 23). One-year measurements of radon concentrations in the subjects' last dwelling were obtained by alpha-track detectors, and the time-weighted average of radon concentrations measured in the bed- and living room was calculated. Dietary habits were recorded with a food frequency questionnaire. Indicator variables of consumption of salad, raw carrots, or fruits (0 = less than daily, 1 = almost daily) were used for adjustment. A positive family history of lung cancer was defined if at least one parent or sibling was reported as having had lung cancer. As an indicator for social class we used the years of school attendance (0 = less than 10 years, 1 = 10 or more years). A previous lung disease was defined if a subject reported a former diagnosis of emphysema, chronic bronchitis, asthma, or tuberculosis. To avoid misclassification due to different pathologists, diagnoses of tumor histology from the reference pathologist were used when available, with missing reference histology replaced by the diagnoses from the clinical pathologist. Histologic type was stratified in adenocarcinoma and other (defined as small cell lung cancer, squamous cell carcinoma, large cell carcinoma, and mixed) types.

Statistical methods

Odds ratios and 95 percent confidence intervals were calculated from unconditional logistic regression models. All analyses were adjusted for sex, age (continuous variable), and region (three regions). Additional terms entered into the regression models were occupational exposure (ever/never), indoor radon exposure (continuous variable), consumption of salad, raw carrots or fruits, family history of lung cancer, previous lung disease, and social class. Since there was no clear indication of confounding, we report results adjusted for age, sex, and region. We performed two-tailed trend tests of a linear trend variable that included the reference category. The trend variable assumed the values corresponding to the median of each exposure category. In addition, analyses were performed after stratification for sex and histologic type.

RESULTS

The study population consisted of 292 lung cancer patients and 1,338 controls. The basic demographic characteristics of the study population are presented in table 1. Twenty percent of the case subjects and 60 percent of the control subjects were men. The mean age was 58 years for male cases and 59 years for male controls; for females, it was 60 years for cases and 62 years for controls. Adenocarcinoma was the most common cell subtype in both male nonsmokers (59 percent) and female nonsmokers (59 percent), followed by squamous cell carcinoma (males, 19 percent; females, 20 percent), small cell lung cancer (males, 16 percent; females, 14 percent), and other (males, 7 percent; females, 7 percent). Compared with controls, lung cancer cases tended to have a lower level of education for both sexes.

ETS exposure during childhood

There was little evidence of increased lung cancer risk associated with ETS exposure in childhood (table 2). A total of 182 cases and 862 controls reported ever having been exposed to ETS in childhood, for an odds ratio of 0.84 (95 percent CI: 0.63, 1.11). This lack of association was also apparent if considering the dichotomous variable of childhood exposure from the father (OR = 0.83; 95 percent CI: 0.62, 1.11) and from the mother (OR = 0.62; 95 percent CI: 0.27, 1.44). There was no trend in risk according to duration of exposure in hours. Restricting the analyses to women yielded results similar to those based on the whole study population.

ETS exposure from the spouse

A total of 144 cases and 395 controls reported that their spouse had ever smoked in their presence (table 3), with an odds ratio of 0.99 (95 percent CI: 0.73, 1.34). No trend was present for cumulative exposure (in pack-years). In terms of duration of exposure in hours, the highest category was associated with a 77 percent excess risk, but the trend test did not achieve statistical significance. About 9 percent of both male cases and controls were ever exposed to smoke by their wives, in contrast to about 59 percent of women, who reported exposure to smoke by their husbands. However, when analyses were restricted to women, results were similar to those of all subjects. Analyses in the group of men were not presented because of insufficient numbers of exposed subjects. The risk estimates of all indicators of spousal ETS exposure were nearly similar within the histopathologic subgroups. For example, the odds ratio for ever exposure was 1.05

TABLE 1. Characteristics of lifetime nonsmokers by sex, Germany, 1990–1996

	Men		Women		Total	
	Cases (n = 58)	Controls (n = 803)	Cases (n = 234)	Controls (n = 535)	Cases (n = 292)	Controls (n = 1,338)
Age in years (%)						
<50	19.0	12.1	3.9	10.5	6.9	11.4
50–54	15.5	14.9	10.7	15.7	11.6	15.3
55–59	27.6	25.2	25.2	18.5	25.7	22.5
60–64	17.2	22.2	15.4	16.3	15.8	19.8
65–69	10.3	16.3	22.2	17.9	19.9	17.0
70–74	10.3	9.3	22.7	21.1	20.2	14.1
Family status (%)						
Single	3.2	3.0	4.5	7.3	4.3	4.7
Married	95.2	91.6	68.2	63.6	73.7	80.6
Widowed		3.0	22.3	21.5	17.8	10.3
Divorced	1.6	2.4	5.0	7.3	4.3	4.4
Years of school attendance (%)						
<9 years of school	1.6	0.8	2.1	1.3	2.0	1.0
9 years	62.9	57.7	78.9	69.0	75.7	62.1
10–11 years	22.6	16.0	10.3	18.6	12.8	17.0
≥12 years	12.9	25.5	8.7	11.1	9.5	19.9
Histologic type (%)						
Squamous cell carcinoma	19.0		19.7		19.5	
Small cell carcinoma	15.5		13.7		14.0	
Adenocarcinoma	58.6		59.4		59.3	
Other histologic type	6.9		7.3		7.2	

(95 percent CI: 0.73, 1.52) for adenocarcinoma of the lung and 0.91 (95 percent CI: 0.59, 1.41) for lung carcinoma other than the adenocarcinoma. A total of 11 case subjects and 70 control subjects who were not exposed to spousal smoke reported exposure to ETS from other cohabitants during their adult life. Overall, subjects who were ever exposed at home during adulthood (spouse or other cohabitants) had an odds ratio of 0.98 (95 percent CI: 0.73, 1.32). No increased risk was associated with increasing duration of smoke exposure in hours or pack-years. This also holds true when restricting analyses to women.

ETS exposure at the workplace

A total of 55 percent of the cases and 63 percent of the controls reported ever being exposed to ETS at the workplace (table 4), yielding an odds ratio of 1.03 (95 percent CI: 0.78, 1.36). No increase in risk with increasing duration of exposure in hours was observed, whereas the highest category of exposure in terms of weighted duration (hours × level of smokiness) showed a nearly twofold significantly increased risk. The pattern of response was similar in the two histologic subgroups; however, the tests of trend for

TABLE 2. Adjusted odds ratios for lung cancer and environmental tobacco smoke exposure during childhood (up to age 18), Germany, 1990–1996

	All subjects					Women				
	Cases (no.)	Controls (no.)	OR*	95% CI*	p for trend	Cases (no.)	Controls (no.)	OR	95% CI	p for trend
Ever exposed										
No	110	476	1.00			88	171	1.00		
Yes	182	862	0.84	0.63, 1.11		146	364	0.78	0.56, 1.08	
Duration of exposure (in hours)										
0–12,000	235	1,124	1.00			188	452	1.00		
>12,000–22,500	22	103	1.06	0.63, 1.76		16	39	0.94	0.51, 1.73	
>22,500	16	85	0.92	0.51, 1.65		13	33	0.97	0.49, 1.90	
Missing values	19	26			0.89	17	11			0.86

* OR, odds ratio adjusted for age, sex, and region; CI, confidence interval.

TABLE 3. Adjusted odds ratios for lung cancer and environmental tobacco smoke exposure to spouse, Germany, 1990–1996

	All subjects					Women				
	Cases (no.)	Controls (no.)	OR*	95% CI*	*p* for trend	Cases (no.)	Controls (no.)	OR	95% CI	*p* for trend
Ever exposed										
No	148	943	1.00			95	219	1.00		
Yes	144	395	0.99	0.73, 1.34		139	316	0.96	0.70, 1.33	
Duration of exposure (in hours)										
0–49,400	218	1,216	1.00			161	431	1.00		
>49,400–67,900	16	54	0.95	0.52, 1.74		16	47	0.98	0.53, 1.81	
>67,900	23	36	1.77	1.00, 3.13		23	33	1.69	0.94, 3.03	
Missing values	35	32			0.13	34	24			0.16
Cumulative exposure (pack-years)										
0–10.0	242	1,236	1.00			185	448	1.00		
10.1–23.0	17	59	0.91	0.51, 1.63		16	49	0.85	0.46, 1.57	
>23	10	25	1.06	0.49, 2.27		10	24	1.03	0.48, 2.24	
Missing values	23	18			0.96	23	14			0.85

* OR, odds ratio adjusted for age, sex, and region; CI, confidence interval.

weighted duration were statistically significant only in the subgroup of lung carcinoma other than adenocarcinoma ($p < 0.05$). When subjects were stratified by sex, the odds ratio for ever exposure at the workplace was 1.14 (95 percent CI: 0.83, 1.57) among women compared with 0.78 (95 percent CI: 0.44, 1.38) among men. Considering women, a statistically significant trend was found for weighted duration, which was even more pronounced when the level of smokiness was ignored. The corresponding risk estimate for highly exposed women was increased nearly threefold.

ETS exposure in vehicles or indoor public settings

Table 5 shows that only a small proportion of about 12 percent of cases and controls reported ever exposure to ETS in vehicles, which was associated with a nonsignificant excess risk of 15 percent. Elevations in risks, however, were associated with weighted duration of exposure in hours. Many more men than women reported ever exposure to ETS in social settings (bars, restaurants). When duration of exposure was considered, no increased risk was observed in analyses with men and women combined or separated

TABLE 4. Adjusted odds ratios for lung cancer and environmental tobacco smoke exposure at the workplace, Germany, 1990–1996

	All subjects					Women				
	Cases (no.)	Controls (no.)	OR*	95% CI*	*p* for trend	Cases (no.)	Controls (no.)	OR	95% CI	*p* for trend
Ever exposed										
No	131	491	1.00			111	258	1.00		
Yes	161	847	1.03	0.78, 1.36		123	277	1.14	0.83, 1.57	
Duration of exposure (in hours)										
0–29,000	247	1,101	1.00			203	497	1.00		
>29,000–61,000	26	127	1.57	0.97, 2.54		17	26	1.85	0.96, 3.54	
>61,000	13	87	1.36	0.71, 2.61		9	8	2.70	1.01, 7.18	
Missing values	6	23			0.10	5	4			0.01
Weighted duration of exposure (hours × level of smokiness)										
0–56,200	199	873	1.00			162	385	1.00		
>56,200–100,600	11	77	1.09	0.55, 2.19		6	15	1.09	0.41, 2.91	
>100,600	17	55	1.93	1.04, 3.58		13	12	2.52	1.12, 5.71	
Missing values	65	333			0.06	53	123			0.04

* OR, odds ratio adjusted for age, sex, and region; CI, confidence interval.

TABLE 5. Adjusted odds ratios for lung cancer and environmental tobacco smoke exposure in vehicles or indoor public settings (bars, restaurants), Germany, 1990–1996

	All subjects				Women			
	Cases (no.)	Controls (no.)	OR*	95% CI*	Cases (no.)	Controls (no.)	OR	95% CI
Vehicles								
Ever exposed								
No	257	1,171	1.00		210	474	1.00	
Yes	35	167	1.15	0.76, 1.75	24	61	0.96	0.57, 1.60
Weighted duration of exposure (hours × level of smokiness)								
0–10,950	276	1,290	1.00		223	516	1.00	
>10,950	14	33	2.64	1.30, 5.36	10	9	2.63	1.04, 6.68
Missing values	2	15			1	10		
Other indoors†								
Ever exposed								
No	210	884	1.00		180	396	1.00	
Yes	82	454	1.08	0.80, 1.47	54	139	0.95	0.66, 1.38
Weighted duration of exposure (hours × level of smokiness)								
0–11,315	272	1,206	1.00		222	504	1.00	
>11,315–19,710	7	65	0.80	0.35, 1.84	3	15	0.52	0.15, 1.86
>19,710	8	45	1.48	0.65, 3.36	4	7	1.44	0.41, 5.10
Missing values	5	22			5	9		

* OR, odds ratio adjusted for age, sex, and region; CI, confidence interval.
† Social settings like bars and restaurants.

by sex. Ever exposure to one of both sources of ETS (transportation or social settings) was associated with an odds ratio of 1.17 (95 percent CI: 0.88, 1.56), whereas the odds ratio was 2.09 (95 percent CI: 1.19, 3.66) among men and 0.95 (95 percent CI: 0.67, 1.34) among women. The highest category of weighted duration of exposure in hours showed a more than twofold increased lung cancer risk (OR = 2.41; 95 percent CI: 1.24, 4.70).

Summary indicators of exposure to ETS

As shown in table 6, when all sources of exposure to ETS outside the home during adulthood (at the workplace, in vehicles, other public indoors) were considered jointly, a statistically significant lung cancer risk was observed in the group of highly exposed subjects, which was higher in the group of women (OR = 1.99; 95 percent CI: 0.95, 4.15) than among men (OR = 1.51; 95 percent CI: 0.68, 3.37). Taking all sources of exposure together yielded an odds ratio of 1.39 (95 percent CI: 0.96, 2.01) in the highest exposure group. Risk estimates did not differ much within the histologic subgroups, except for women if considering ETS sources other than home. Here a stronger trend in risk was observed in subjects with cancer other than adenocarcinomas than among those with adenocarcinoma.

We have also evaluated the effects of various possible confounders. As an example, table 7 presents the lung cancer risk for subjects highly exposed to the summary indicator of ETS at all sources with further adjustment for occupational exposure; educational level; residential radon; family history of lung cancer; previous lung disease; and consumption of salad, raw carrots, or fruits. There was no evidence that the association of ETS and lung cancer was confounded. This also holds true if considering each source of ETS separately.

DISCUSSION

In this report the lung cancer risk associated with various sources of ETS exposure in nonsmoking men and women was assessed. Our data, indicating no effect of exposure to ETS in childhood, are in concordance with most other studies (15, 17, 24–27). However, there are also epidemiologic studies demonstrating an excess lung cancer risk due to childhood ETS exposure (28–30). Limited power and use of proxy interviews in some of these studies, and particularly the difficulty in recall of exposures far in the past, may contribute to these inconsistencies.

Most of the available studies on ETS exposure and lung cancer concentrated on the exposure to spousal smoking. Ever exposure was associated with an

TABLE 6. Adjusted odds ratios for lung cancer and summary indicators of environmental tobacco smoke (ETS) exposure at different sources by histologic type, Germany, 1990–1996

	All subjects				Women			
	Cases (no.)	Controls (no.)	OR*	95% CI*	Cases (no.)	Controls (no.)	OR	95% CI
Exposure to ETS, all sources (hours × level of smokiness)								
All lung carcinoma								
No or low	191	903	1.00		154	362	1.00	
Medium	49	240	0.98	0.68, 1.41	37	105	0.87	0.57, 1.34
High	52	195	1.39	0.96, 2.01	43	68	1.51	0.97, 2.33
Adenocarcinoma								
No or low	110	903	1.00		92	362	1.00	
medium	31	240	1.08	0.70, 1.68	20	105	0.75	0.46, 1.34
High	32	195	1.47	0.94, 2.30	27	68	1.56	0.93, 2.59
Other carcinomas								
No or low	81	903	1.00		62	362	1.00	
Medium	18	240	0.84	0.47, 1.42	17	105	1.01	0.56, 1.81
High	20	195	1.33	0.78, 2.28	16	68	1.49	0.80, 2.77
Exposure to ETS, sources other than home† (hours × level of smokiness)								
All lung carcinoma								
No or low	245	1,101	1.00		203	483	1.00	
Medium	25	140	1.29	0.79, 2.09	17	34	1.38	0.74, 2.57
High	22	97	1.78	1.05, 3.04	14	18	1.99	0.95, 4.15
Adenocarcinoma								
No or low	147	1,101	1.00		124	483	1.00	
Medium	13	140	1.14	0.61, 2.13	7	34	0.92	0.39, 2.17
High	13	97	1.77	0.92, 3.41	8	18	1.83	0.76, 4.39
Other carcinomas								
No or low	98	1,101	1.00		79	483	1.00	
Medium	12	140	1.58	0.81, 3.06	10	34	2.22	1.03, 4.80
High	9	97	1.89	0.88, 4.06	6	18	2.35	0.88, 6.80

* OR, odds ratio adjusted for age, sex, and region; CI, confidence interval.
† Other sources: workplace, other indoors (e.g., restaurants), and in vehicles.

TABLE 7. Effects of potential confounders on the risk estimate for subjects highly exposed to environmental tobacco smoke (ETS) exposure at all sources, Germany, 1990–1996

	OR*	95% CI*
Model 1†	1.39	0.96, 2.01
Model 1 + adjustment for social class	1.35	0.93, 1.95
Model 1 + adjustment for family history of lung cancer	1.39	0.96, 2.02
Model 1 + adjustment for occupational carcinogens	1.41	0.97, 2.04
Model 1 + adjustment for residential radon	1.37	0.95, 1.99
Model 1 + adjustment for previous lung disease	1.39	0.96, 2.01
Model 1 + adjustment for consumption of raw carrots	1.38	0.95, 2.00
Model 1 + adjustment for consumption of salad	1.38	0.96, 2.01
Model 1 + adjustment for consumption of fresh fruits	1.39	0.96, 2.01

* OR, odds ratio; CI, confidence interval.
† Model 1: logistic regression for the highest category of ETS exposure to all sources adjusted for age, sex, and region (see table 6).

increased lung cancer risk in the majority of these studies, but risk estimates were statistically significant in only a few single studies (25, 27, 31). The meta-analysis of 37 studies by Hackshaw et al. (2), however, provided a summary risk of 1.24 (95 percent CI: 1.13, 1.36) among women and an odds ratio of 1.34 (95 percent CI: 0.97, 1.84) among men. In the European multicenter study (17), an odds ratio of 1.16 (95 percent CI: 0.93, 1.44) was observed, which is close to the combined relative risk of 1.17 (95 percent CI: 0.84, 1.62) of the US Environmental Protection Agency (3), while no elevated risk was noted for this variable in the present study. A significant trend or an elevated odds ratio in the highest category of ETS exposure with respect to average number of smoked cigarettes or pack-years was reported in several studies (9, 11, 24, 28, 32, 33). In the European multicenter study (17), an odds ratio of 1.80 (95 percent CI: 1.12, 2.90) for the highest category of the variable duration in hours was observed. This odds ratio is comparable with ours (OR = 1.77) and that of the other German study (OR = 1.87;

95 percent CI: 0.45, 7.74 among never smokers) (15). When considering pack-years, we observed no odds ratio different from one in our study, whereas the study from the International Agency for Research on Cancer (17) found an elevated risk in the highest category of pack-years.

Up to now workplace ETS exposure has received less attention than residential ETS exposure, and results were inconsistent among the few studies. Some report no association (24, 26, 27, 34), while others suggest a relation between ETS exposure at the workplace and lung cancer (13, 15, 21). The present study indicates evidence for an excess risk due to ETS at the workplace, particularly among women. The less quantitative variable of duration in hours weighted by the level of smokiness resulted in a twofold significantly increased lung cancer risk for highly exposed subjects overall and an odds ratio of 2.5 among women, respectively. It is difficult to determine whether this more subjective measure is a valid index for estimating exposure, but the even more pronounced odds ratio among highly exposed women, when the level of smokiness was excluded, serves to increase confidence in the results. The same subjective index was used in two other European studies, yielding an odds ratio of 2.07 (95 percent CI: 1.33, 3.21) among highly exposed subjects in the study from the International Agency for Research on Cancer (17) and an odds ratio of 2.67 (95 percent CI: 0.74, 9.67) in the other German study (15).

A significantly increased trend in risk was observed in the present study for weighted duration of ETS exposure in transportation and if considering ETS exposure in transportation and social settings jointly. An elevated lung cancer risk due to ETS exposure in vehicles among women was also noted by Kabat et al. (24), while the European multicenter study (17) found no association to either transportation or social settings. Fontham et al. (25) reported odds ratios somewhat higher for exposure in occupational and social settings than within households, which is consistent with our results and those of Jöckel et al. (15). These results may reflect chance, recall bias, or the potential of a larger number of smokers and therefore of higher exposures in these public settings (25), which is supported by measurements of indoor air in bars, restaurants, and trains (35).

Limitations and strengths of the present study

Our study has several major strengths. These include the large sample size, one of the largest series of nonsmoking lung cancer cases in a single study to date. All interviews were conducted with the subjects themselves in face-to-face interviews, in contrast to studies in which surrogates were used. In addition, we used a standardized questionnaire, which enables us to investigate various sources of ETS exposure at home and in public places, in childhood and adulthood. Misclassification of disease status was minimized by the inclusion criteria of microscopic diagnosis and an independent review of diagnosed material that was completed for 75 percent of the cases. Moreover, we controlled for most potential confounders.

Nevertheless there are several limitations in our study. Particular concern has to be given to potential biases, such as selection of cases and controls, misclassification of nonsmoking status, misclassification of ETS exposure, and confounding. Nonsmoking status was not validated in our study. Results of a European validation study using cross-interviews with next of kin suggest that bias from nonsmoker misclassification is likely to be nonsignificant. Of 405 index subjects, only five were falsely classified as nonsmokers (36). This validation study was part of the multicenter study from the International Agency for Research on Cancer (17) that used the same questionnaire and criteria for definition of nonsmokers as in the present study. If we apply the percentages to our study, about 23 controls and 3–4 cases may have been incorrectly classified as nonsmokers.

Another possible source of bias is the misclassification of exposure to ETS (7, 37). Presently, past exposure to ETS can only be estimated through interview data since the known biologic markers (e.g., cotinine) are short-lived and cannot document exposures that occurred in years past. One method of validation of self-reported ETS exposure is conducting interviews with relatives on ETS exposure. Using this approach, Nyberg et al. (38) found a high correlation between cumulative consumption by the spouse and the information reported by the study subjects (Spearman's correlation coefficient = 0.92). To measure the reliability of ETS exposure histories, Brownson et al. (39) conducted reinterviews for 110 subjects. A high agreement for parental smoking status (95 percent concordance), spousal smoking status (84 percent concordance), and cigarette pack-years was noted, while a Canadian study (40) has demonstrated that residential exposure to ETS is more reliable than occupational exposure and that quantitative measures such as duration were even less reliable.

Given the weak associations observed between lung cancer and ETS, potential confounding factors must be considered. We found no evidence that the observed asociations of lung cancer risk and ETS were explained by confounders such as occupation, education, radon, previous lung disease, or a family history of cancer. Although it has been suggested that a low intake of carotenoids and a high intake of dietary fat

are potential confounders (41), this was not observed in our study or in other recently published studies (15, 17, 25). Hackshaw (42) recently evaluated 37 epidemiologic studies on lung cancer and ETS. He reported that all eight studies that included information on dietary habits have found that the effect of dietary confounding was negligible.

Some potential methodological problems in our study concern the recruitment of cases and the low response rates among controls. Up to now there exists no overall cancer registry in Germany. Therefore, patients had to be selected via hospitals. To get an estimate of the coverage, we compared the average number of lung cancer cases per year enrolled from the study hospitals in the eastern study region with data of the former cancer registry in eastern Germany using the average number of lung cancer diseases per year between 1985 and 1990. The coverage was about 50 percent. Since we have no information on possible risk factors of the overall lung cancer cases, the extent of representativeness of our cases to all cases is not measurable. However, the advantage of hospital-based cases is that patients were alive at interview and no surrogate interviews had to be used.

To investigate the reasons for the low response rates among population controls, we conducted a nonresponse analysis in a subsample of refusals. 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 (19). We do not believe that our results were explained by selection bias, because our findings were highly consistent with those of a case-control study on ETS and lung cancer conducted in the northern parts of Germany (15). In this study, the same questionnaire and approach of quantification were used as in our study, and a twofold significantly increased lung cancer risk for ETS at the workplace or in other public settings and no significantly increased association for ETS in childhood or ETS by spouse were observed.

In conclusion, our study suggests that a high exposure to ETS is associated with a small, but consistent increased lung cancer risk. In addition to the established risk due to household ETS, exposures at the workplace and other public places appear to be important risk factors for lung cancer among nonsmokers in our study.

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