

# ARTICLES

## Multicenter Case–Control Study of Exposure to Environmental Tobacco Smoke and Lung Cancer in Europe

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**Background:** An association between exposure to environmental tobacco smoke (ETS) and lung cancer risk has been suggested. To evaluate this possible association better, researchers need more precise estimates of risk, the relative contribution of different sources of ETS, and the effect of ETS exposure on different histologic types of lung cancer. To address these issues, we have conducted a case–control study of lung cancer and exposure to ETS in 12 centers from seven European countries. **Methods:** A total of 650 patients with lung cancer and 1542 control subjects up to 74 years of age were interviewed about exposure to ETS. Neither case subjects nor control subjects had smoked more than 400 cigarettes in their lifetime. **Results:** ETS exposure during childhood was not associated with an increased risk of lung cancer (odds ratio [OR] for ever exposure = 0.78; 95% confidence interval [CI] = 0.64–0.96). The OR for ever exposure to spousal ETS was 1.16 (95% CI = 0.93–1.44). No clear dose–response relationship could be demonstrated for cumulative spousal ETS exposure. The OR for ever exposure to workplace ETS was 1.17 (95% CI = 0.94–1.45), with possible evidence of increasing risk for increasing duration of exposure. No increase in risk was detected in subjects whose exposure to spousal or workplace ETS ended more than 15 years earlier. Ever exposure to ETS from other sources was not associated with lung cancer risk. Risks from combined exposure to spousal and workplace ETS were higher for squamous cell carcinoma and small-cell carcinoma than for adenocarcinoma, but the differences were not statistically significant. **Conclusions:** Our results indicate no association between childhood exposure to ETS and lung cancer risk. We did find weak evidence of a dose–response relationship between risk of lung cancer and exposure to spousal and workplace ETS. There was no detectable risk after cessation of exposure. [J Natl Cancer Inst 1998;90:1440–50]

During the last 15 years, epidemiologic studies have been conducted on the association between exposure to environmen-

tal tobacco smoke (ETS) and lung cancer. Several authors and regulatory agencies have concluded that a causal link has been established [e.g., see (1–3)], whereas some authors consider that bias and confounding factors constitute a plausible explanation for the observed association [e.g., see (4)]. The available studies are—in most cases—too small to adequately assess the magnitude of the effect and to address specific aspects, such as the shape of the dose–response relationship, the effect of cessation of exposure, the importance of multiple sources of ETS exposure, and the interaction of ETS exposure with other risk factors of lung cancer. Furthermore, relatively few studies of such exposure are available from Europe (5–10). Characteristic of tobacco smoking in European countries are the mixed consumption of blond and black tobacco cigarettes (11) and the low prevalence—at least in the past—of smoking among women compared with men (12).

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Since 1988, the International Agency for Research on Cancer (IARC) has coordinated an international, multicenter, case-control study of lung cancer in nonsmokers. The main objective of this study was to provide an estimate of the risk of lung cancer from exposure to ETS in western European populations that would be more precise than estimates available at that time. Secondary objectives of the study were to address more detailed aspects of the association between ETS and lung cancer and to study the role of factors other than ETS in lung carcinogenesis in nonsmokers. The study was designed originally to have a statistical power of 80% to detect a relative risk of 1.3 (at a 5% level of statistical significance) for an exposure with a prevalence of 40% and a control-to-case subject ratio of 2 (required number of case subjects, 572). Herein, we report the principal findings of this study. Results of a study from Sweden that partially overlaps with ours have been published recently (13). Detailed results of our multicenter study, stratified by sex, age, center, and histologic type, are available from IARC<sup>1</sup>.

## SUBJECTS AND METHODS

Twelve centers from seven European countries participated in a multicenter, case-control study of lung cancer in never smokers—Germany 1 (Bremen and Frankfurt metropolitan areas), Germany 2 (parts of North Rhine-Westphalia, Eifel, and Saarland), Germany 3 (Thuringia and Saxony), Sweden (Stockholm county), U.K. (Devon and Cornwall), Spain (Barcelona metropolitan area), Italy 1 (Turin), Italy 2 (five areas in the Veneto region), Italy 3 (patients from one hospital in Rome), France (patients from 12 hospitals, of which nine are in Paris), Portugal 1 (patients from three hospitals in Lisbon), and Portugal 2 (patients from one hospital in Vila Nova de Gaia [Porto]).

Details of the study design varied among the centers. The period of enrollment of case and control subjects was from 1988 to 1994. The most important difference in the study design among the centers was the selection of control subjects. Control subjects were hospital based in the centers from France, Portugal, Spain, and one of the Italian centers (Italy 3); control subjects were both hospital and community based in the center from the U.K.; and control subjects were community based in the other centers. Community-based control subjects were selected from population registers. The diagnoses of hospital-based control subjects varied among the centers, but patients with smoking-related diseases were excluded from the control series in all centers. There were minor differences among centers in terms of age restriction and diagnostic criteria for case eligibility. Some centers had no age restriction, whereas other centers excluded subjects aged 75 years or older. This combined analysis is restricted to case and control subjects up to age 74 years. Smokers were studied in all but the Portuguese centers. In selected centers, case subjects without a histologic or a cytologic diagnosis were also included.

Case and control subjects were interviewed by use of a common questionnaire designed to gather details on ETS exposure during childhood and during adulthood at home, at the workplace, in vehicles, and in public places. The questionnaire had been developed on the basis of the results of a study on urinary cotinine levels and ETS exposure (14). The common questionnaire also included sections on demographic variables, residential history (including a history of the subject's cooking and heating arrangements), and exposure to known and suspected occupational lung carcinogens (15). In addition, the centers from Germany, Sweden, Spain, the U.K., France, and one center from Italy collected information on dietary habits—from which were derived indicators of intake of vegetables, fruits,  $\beta$ -carotene, total carotenoids, and retinol.

A screening questionnaire was used to determine the history of smoking by case and control subjects, and emphasis was placed on quantifying occasional smoking. Only those subjects who reported that they had not smoked more than 400 cigarettes during their life were eligible for this study. In three of the centers, a parallel study was carried out to validate the never-smoking status of the index subject. This validation was done by interviewing independently a next of kin on his or her smoking habits and those of the index subject.

Quantitative variables used for childhood ETS exposure (exposure up to age 18 years) included the number of smokers in the household and the cumulative exposure—expressed as the number of years of exposure weighted for the type

of smoker [mother = 1, father = 0.75, and other adults = 0.25; these weights were based on studies of urinary cotinine concentrations in children (16)]. Quantitative variables of exposure to ETS from the spouse within marriage as well as from other cohabitants, such as partners and roommates, included the following: 1) the total number of years of exposure, denoted as duration (in years); 2) the product of the number of years and the number of hours per day of exposure, denoted as duration (in hours/day  $\times$  years); 3) the average number of cigarettes smoked per day by the spouse in the presence of the index subject; and 4) the cumulative exposure, expressed as pack-years and derived from the product of variables 1 and 3 listed above. Spousal cigar and pipe smoke represented a small fraction of total spousal ETS; the variables described above included exposure to all types of tobacco products, expressed as cigarette-equivalents after applying a weight of 2 to cigarillos and 3 to cigars and pipes (17). In preliminary analyses, the use of variables restricted to exposure to cigarette smoke yielded results very similar to those based on the use of variables combining all types of tobacco products. The analysis on spousal ETS exposure was repeated 1) after restriction to subjects ever married and 2) after taking into account also ETS of cohabitants other than the spouse. Quantitative variables for workplace ETS exposure were as follows: 1) the total number of years of exposure and 2) the total number of years of exposure weighted for the number of hours of exposure per day and for a subjective index of smokiness of the workplace. We also derived indicators of duration of exposure and time since cessation of exposure to either spousal or workplace ETS.

For each source of ETS exposure, case and control subjects who were never exposed to ETS from that source comprised the reference category. For each parameterization of ETS exposure, exposed subjects were divided into three categories, defined by the 75th and 90th percentiles of the distribution among control subjects. The choice of the cut point at the 75th percentile was based on the results of a urinary cotinine study conducted in Germany and Poland, which showed a smaller degree of misclassification in the highest quartile compared with the three lowest quartiles of the distribution (18). We performed two-tailed tests for linear trends by testing the significance of the regression parameter of a trend variable that also included the reference category. The trend variable assumed the values corresponding to the median of each exposure category among control subjects.

Logistic regression modeling was the main method chosen for the statistical analysis. In some centers control subjects were individually matched to case subjects on sex and age, whereas in other centers frequency matching was the strategy of choice. Individual matching of case and control subjects requires the fitting of conditional regression models, whereas lack of individual matching permits the use of unconditional modeling (19). The results obtained by use of unconditional logistic regression for all centers and a combination of conditional logistic regression for centers with individual matching and unconditional logistic regression for the other centers (20) were compared. The basic regression model comprised—in addition to the exposure variables of interest—terms for sex, 10-year age groups, center, and the interaction between sex and center. The inclusion of the interaction terms resulted in an improvement of the goodness of fit of most of the regression models. Additional terms—entered into the regression models as potential confounders—were educational level (as a variable with three categories based on center-specific cut points), proportion of life spent in urban areas, occupational exposure to lung carcinogens, and intake of vegetables,  $\beta$ -carotene, total carotenoids, and retinol.

The statistical significance of the difference among the center-specific results was evaluated by a comparison of the deviance of the basic regression model and that of an expanded model containing the interaction term between exposure and center. Additional analyses were performed after case and control subjects were divided according to 1) sex, 2) histologic type of cancer (squamous cell carcinoma, small-cell carcinoma, adenocarcinoma, and other, mixed and undefined histologic types), 3) whether subjects spent more than 75% of their life in urban or in rural areas, and 4) source of control subjects (centers with hospital-based and with population-based control subjects).

## RESULTS

The database for the analysis contained 650 patients with lung cancer, of whom 627 (96.5%) had microscopically confirmed disease, and 1542 control subjects. The response rate for the centers ranged from 55% to more than 95%, with the exception of three centers (Germany 2, Germany 3, and Portugal 2)

in which the response rate among control subjects was lower than 50%. Two of the German centers and the centers in Sweden, France, and Spain contributed the largest numbers of case subjects (Table 1). Of the case subjects and the control subjects, 21.7% and 34.4%, respectively, were men. The distribution of age was very similar among case and control subjects: The mean age was 58 years in male case subjects and 59 years in male control subjects; the corresponding value for both female case and control subjects was 62 years. Adenocarcinoma was the most common histologic type (51.2% of case subjects), whereas squamous cell carcinoma accounted for 16.8% and small-cell carcinoma for 10.8% of case subjects.

In a comparison between the unconditional and the mixed conditional/unconditional approaches for multivariate logistic regression, the results were very similar for most of the variables analyzed (Fig. 1). In the following sections, only results based on unconditional regression modeling are reported.

### Childhood Exposure to ETS

A total of 389 case subjects and 1021 control subjects reported ever having been exposed to ETS during childhood, for an overall odds ratio (OR) of 0.78 (95% CI = 0.64–0.96) (Table 2). In all but three centers, the OR was below 1.0 (Fig. 2, A). The *P* value of the test for heterogeneity among centers was .49. Subjects' fathers were more likely to be smokers than subjects' mothers. The risk estimate was similar for exposure to ETS from the father and the mother; the estimated OR for exposure to ETS from the father was 0.76 (95% CI = 0.61–0.94), whereas that for exposure to ETS from the mother was 0.92 (95% CI = 0.57–1.49). There was no trend in risk according to number of smokers in the household, and there was a decreasing trend

according to cumulative exposure, expressed either as smoker-years or weighted smoker-years (Table 2). The risk of lung cancer from exposure to ETS during childhood was similar in men and women. No pattern emerged according to age at diagnosis or histologic type of lung cancer.

Results similar to those based on the whole study population, although more unstable because of small numbers in the various categories, were obtained after exclusion of men (Table 2) or subjects who reported exposure to ETS during adulthood. When exposure to ETS in childhood was subdivided into two periods—from birth (age 0 years) to 10 years and from age 11 years to 18 years—to take into account the different status of the growth of the lung, the results for either period were similar to those for childhood overall.

### Exposure to ETS From the Spouse

The ORs for subjects who were ever married to a smoker were 1.27 (95% CI = 1.00–1.62) in the overall population, 1.20 (95% CI = 0.92–1.55) among women, and 1.65 (95% CI = 0.85–3.18) among men. A related variable, self-reported exposure to spousal smoke, was used as the main indicator for this source of ETS; 344 case subjects and 700 control subjects reported ever having had such exposure, yielding an OR of 1.16 (95% CI = 0.93–1.44) (Table 3). The 12 centers in the study showed some heterogeneity in the risk estimate for this variable, with an OR higher than 1.5 in four centers and an OR lower than 0.7 in one center. The tests of heterogeneity performed on center-specific results, however, did not suggest significant differences (*P* = .42). The exclusion of case and control subjects who were never married reduced the study population by about 24%, but it did not materially affect the results (OR for ever exposure to spousal smoke = 1.18; 95% CI = 0.92–1.51). Most of the exposure came from cigarettes; 12 case subjects and 27 control subjects were exposed to ETS from cigar and pipe only.

There was an increasing risk of lung cancer with increasing duration (in hours/day × years) of exposure (Table 3), whereas only weak evidence of a trend emerged for cumulative exposure; no trend was present for duration of exposure (in years) and for average exposure (cigarettes/day). When we repeated the test for trend without the reference category, the *P* values were .004 for duration (in hours/day × years) of exposure and .07 for cumulative exposure. These results were similar, although less precise, when the analysis was restricted to women (Table 3).

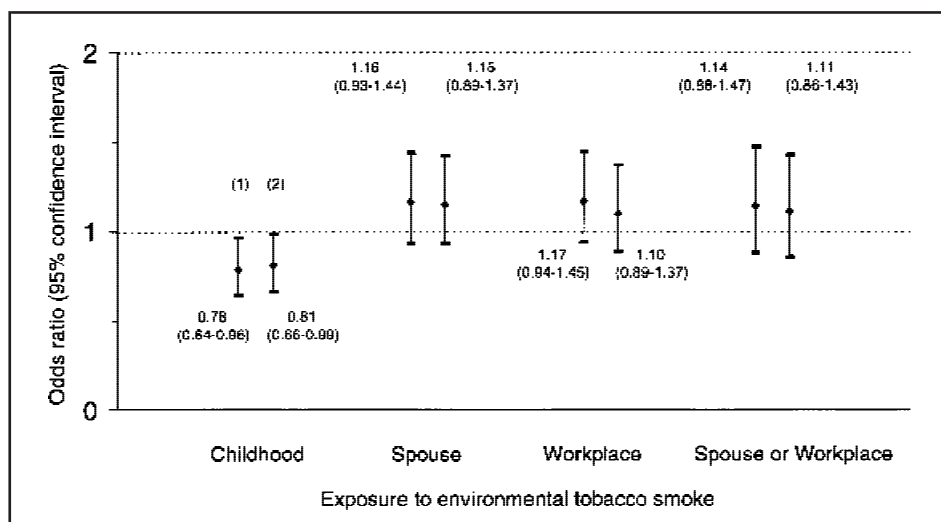
The analysis by type of tobacco product smoked by the spouse was hampered by the small number of case and control subjects who reported exposure to smoke from cigar and pipe only. The OR in this group was 0.84 (95% CI = 0.41–1.73), whereas the ORs for ever exposure to ETS from cigarettes were similar to those for ever exposure to ETS from any type of tobacco product.

Other potential risk factors of lung cancer exerted only a minor confounding effect on the association between exposure to spousal smoke and lung cancer. As an example, the OR for ever exposure to spousal ETS (1.16 [95% CI = 0.93–1.44], Table 3) was modified to 1.18 (95% CI = 0.94–1.46) after further adjustment for exposure to suspected or known occupational lung carcinogens, to 1.15 (95% CI = 0.91–1.45) after adjustment for urban, rural, or mixed urban and rural residence

**Table 1.** Selected characteristics of case and control subjects

	Case subjects (n = 650)		Control subjects (n = 1542)	
	No.	%	No.	%
<b>Study center</b>				
Sweden	70	10.8	112	7.3
Germany 1	76	11.7	229	14.9
Germany 2	142	21.8	163	10.6
Germany 3	31	4.8	52	3.4
U.K.	26	4.0	140	9.1
France	77	11.8	151	9.8
Portugal 1	49	7.5	39	2.5
Portugal 2	33	5.1	53	3.4
Spain	71	10.9	159	10.3
Italy 1	40	6.2	221	14.3
Italy 2	19	2.9	173	11.2
Italy 3	16	2.5	50	3.2
<b>Sex</b>				
Female	509	78.3	1011	65.6
Male	141	21.7	531	34.4
<b>Age, y</b>				
<55	165	25.4	361	23.4
55–64	210	32.3	552	35.8
65–74	275	42.3	629	40.8
<b>Histologic type</b>				
Squamous cell carcinoma	109	16.8	—	—
Adenocarcinoma	333	51.2	—	—
Small-cell carcinoma	70	10.8	—	—
Other histologic type	115	17.7	—	—
Unknown	23	3.5	—	—

**Fig. 1.** Results of comparisons of exposure to environmental tobacco smoke for childhood, spouse, workplace, and spouse or workplace, by use of two different approaches: (1) unconditional logistic regression adjusted for age and for interaction between sex and center and (2) combination of unconditional logistic regression in centers without individual matching and conditional logistic regression stratified on the matched sets in centers with individual matching.



**Table 2.** Odds ratios of lung cancer from exposure to environmental tobacco smoke during childhood

	All subjects*					Women*				
	Case subjects	Control subjects	OR	95% CI	P for trend†	Case subjects	Control subjects	OR	95% CI	P for trend†
Ever exposed										
No	252	496	1.00	Referent		187	295	1.00	Referent	
Yes	389	1021	0.78	0.64–0.96		314	700	0.77	0.61–0.98	
Missing values	9	25				8	16			
No. of smokers in household										
None	252	496	1.00	Referent		187	295	1.00	Referent	
1	305	750	0.80	0.64–0.99		243	528	0.76	0.59–0.98	
2	52	191	0.63	0.44–0.90		43	117	0.69	0.46–1.04	
≥3	32	80	1.05	0.65–1.70	.24	28	55	1.13	0.67–1.91	.54
Missing values	9	25				8	16			
Cumulative exposure (weighted smoker-years‡)										
0	252	496	1.00	Referent		187	295	1.00	Referent	
0.1–14.0	248	582	0.83	0.66–1.04		193	394	0.78	0.60–1.02	
14.1–18.0	104	332	0.68	0.51–0.92		93	239	0.73	0.53–1.02	
≥18.1	37	107	0.80	0.51–1.24	.02	28	67	0.90	0.54–1.50	.10
Missing values	9	25				8	16			

\*OR = odds ratio adjusted for age and sex–center interaction; CI = confidence interval.

†Two-tailed P value of test for linear trend.

‡See text for details on weights.

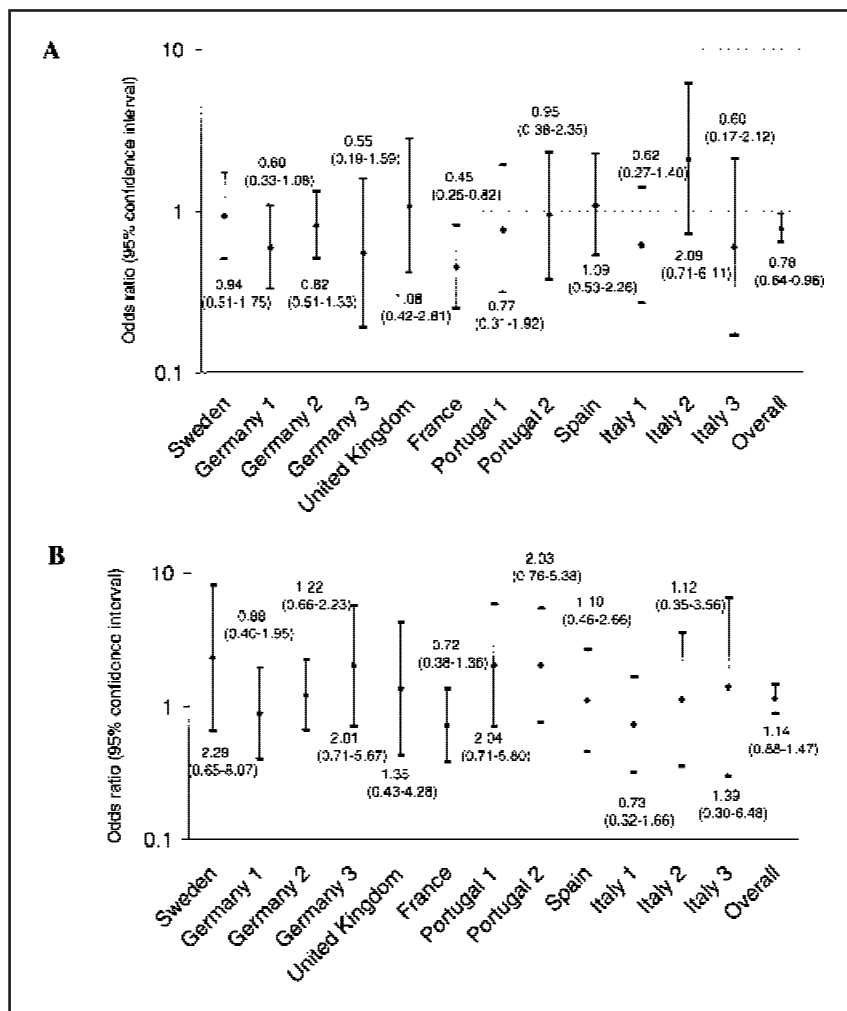
during the last 35 years, and to 1.14 (95% CI = 0.89–1.45) after adjustment for consumption of vegetables above or below the median level.

When study subjects were stratified by sex, the OR for ever exposure to spousal smoke was 1.47 (95% CI = 0.81–2.66, based on 23 exposed case subjects and 68 exposed control subjects) among men, compared with 1.11 (95% CI = 0.88–1.39) among women (Table 3). The small number of exposed men hampered more detailed quantitative analyses. When we stratified the data by age of the subject at interview, no increase in risk was present among subjects aged less than 55 years (OR = 0.99; 95% CI = 0.64–1.52), whereas the ORs were 1.19 (95% CI = 0.80–1.76) among subjects aged 55–64 years and 1.25 (95% CI = 0.89–1.75) among subjects aged 65–74 years.

The association between lung cancer and exposure to ETS from the spouse was nonsignificantly stronger for squamous cell carcinoma and small-cell carcinoma than for adenocarcinoma (OR for squamous cell carcinoma [n = 59] = 1.21 [95% CI =

0.77–1.91]; OR for small-cell carcinoma [n = 39] = 1.39 [95% CI = 0.79–2.45]; and OR for adenocarcinoma [n = 174] = 1.08 [95% CI = 0.82–1.42]). For all major histologic types, a dose–response relationship was suggested with cumulative exposure and duration (in hours/day × years) of exposure to spousal smoke (results not shown). This pattern was visible more clearly for squamous cell carcinoma than for adenocarcinoma. The small number of cases of small-cell carcinoma limited the precision of the risk estimates for this histologic type.

The questionnaire included questions on smoking habits of cohabitants other than the spouse during the adult life of the study subjects. A total of 44 (6.8%) case subjects and 123 (8.0%) control subjects who were not exposed to spousal smoke reported this source of exposure to ETS. The risk estimates from exposure to ETS from any cohabitant tended to be somewhat lower than those from exposure to spousal smoke only (OR for ever exposed = 1.10 [95% CI = 0.88–1.36]; ORs for cumulative exposure = 0.96 [95% CI = 0.74–1.23] for 0.1–13.0 pack-



**Fig. 2.** Center-specific odds ratios and 95% confidence intervals (bars) for environmental tobacco smoke exposure. **A)** Childhood environmental tobacco smoke. Test for heterogeneity among centers:  $\chi^2 = 10.45$ ; degrees of freedom (df) = 11;  $P = .49$ . **B)** Combined environmental tobacco smoke from the spouse or at the workplace. Test for heterogeneity among centers:  $\chi^2 = 6.76$ ; df = 11;  $P = .82$ .

years, 1.02 [95% CI = 0.66–1.59] for 13.1–25.0 pack-years, and 1.37 [95% CI = 0.85–2.20] for  $\geq 25.1$  pack-years).

### Exposure to ETS at the Workplace

A total of 374 case subjects and 855 control subjects reported ever exposure to ETS at the workplace, yielding an OR of 1.17 (95% CI = 0.94–1.45) (Table 4). The risk estimates in eight centers were above 1.0, and the risk estimates showed no statistically significant heterogeneity ( $P = .23$ ). The trend analyses for weighted duration of exposure, but not for unweighted duration of exposure, showed an increasing risk in the whole study population as well as in women (Table 4). Exposure at the workplace resulted in a similar risk estimate in men (OR = 1.13 [95% CI = 0.68–1.86], based on 105 exposed case subjects and 379 exposed control subjects) and in women (OR = 1.19; 95% CI = 0.94–1.51); a similar pattern was found for duration of exposure to ETS at the workplace. No pattern was found according to age at interview. The OR of ever exposure to ETS at the workplace was higher for squamous cell carcinoma (OR = 1.27; 95% CI = 0.82–1.97) than for adenocarcinoma (OR = 1.06; 95% CI = 0.81–1.40) or small-cell carcinoma (OR =

1.17; 95% CI = 0.67–2.04), although this difference was not statistically significant. The potential confounders—educational level, residence in urban areas, exposure to occupational carcinogens, and intake of vegetables, retinoids, and carotenoids—had no appreciable effect on the ORs of exposure to ETS at the workplace.

### Combined Spousal and Workplace ETS Exposure

Ever exposure to either of the two major sources of ETS—the spouse and the workplace—was associated with an OR of 1.14 (95% CI = 0.88–1.47) (Table 5); there was no significant heterogeneity among centers ( $P = .82$ ) (Fig. 2, B). A weak increase in lung cancer risk was present for increasing duration of exposure (Table 5). The trend was stronger for duration (in hours/day  $\times$  years) of exposure and was present also in the analysis restricted to women (Table 5). Having had past ETS exposure from either of these two sources, but no exposure for at least 15 years, was not associated with an increased risk of lung cancer (Table 5). The ORs of exposure to either source were similar in men (OR = 1.13; 95% CI = 0.68–1.89) and women (OR = 1.15; 95% CI = 0.86–1.55) and were higher among subjects aged 65 years or more than among younger subjects.

Duration (in years) and duration (in hours/day  $\times$  years) of exposure to ETS from either source were associated with an increased risk of squamous cell carcinoma and small-cell carcinoma but not of adenocarcinoma (Table 6). For both squamous cell carcinoma and small-cell carcinoma, a decrease in risk with time since cessation of exposure was present (Table 6).

### Exposure to ETS in Vehicles and Public Indoor Settings

The results for variables representing two further sources of exposure to ETS—vehicles and other public indoor settings—were not consistent among the centers. The range of center-specific ORs for exposure in vehicles (based on a total of 125 exposed case subjects and 310 exposed control subjects) ranged from 0 to 2.85, with an overall estimate of 1.14 (95% CI = 0.88–1.48). The range of estimates for ETS exposure in public indoor settings such as restaurants (174 exposed case subjects and 454 exposed control subjects) was 0.24–2.32, with an overall estimate of 1.03 (95% CI = 0.82–1.29). Analyses by duration of exposure did not suggest any consistent pattern for either of these two sources of exposure to ETS.

### DISCUSSION

The results of our study of the risk of lung cancer from ETS in several European countries showed a reduced risk for exposure during childhood and a measurable effect of exposure to ETS from the spouse and at the workplace, in particular when these two sources were combined to better represent total adult

**Table 3.** Odds ratios of lung cancer from exposure to environment tobacco smoke from the spouse

	All subjects*					Women*				
	Case subjects	Control subjects	OR	95% CI	<i>P</i> for trend†	Case subjects	Control subjects	OR	95% CI	<i>P</i> for trend†
Ever exposed										
No	305	838	1.00	Referent		187	376	1.00	Referent	
Yes	344	700	1.16	0.93–1.44		321	632	1.11	0.88–1.39	
Missing values	1	4				1	3			
Duration of exposure (in years)										
Unexposed	305	838	1.00	Referent		187	376	1.00	Referent	
1–34	223	498	1.05	0.83–1.33		202	439	0.99	0.77–1.27	
35–42	65	103	0.63	0.12–2.37		64	98	1.57	1.06–2.31	
≥43	38	80	1.07	0.68–1.68	.10	37	76	1.05	0.66–1.68	.19
Missing values	19	23				19	22			
Duration of exposure (hours/day × years)										
Unexposed	297	778	1.00	Referent		181	327	1.00	Referent	
1–135	165	396	0.90	0.70–1.16		146	348	0.80	0.61–1.06	
136–223	44	81	1.20	0.78–1.85		42	75	1.12	0.72–1.74	
≥224	41	53	1.80	1.12–2.90	.02	41	52	1.70	1.05–2.75	.03
Missing values	103	234				99	209			
Average exposure (cigarettes/day)										
Unexposed	297	778	1.00	Referent		181	327	1.00	Referent	
0.1–10.0	206	411	1.10	0.86–1.40		184	360	1.00	0.77–1.31	
10.1–18.0	25	83	0.58	0.35–0.90		25	79	0.57	0.34–0.93	
≥18.1	35	55	1.37	0.85–2.20	.88	35	52	1.34	0.83–2.17	.97
Missing values	87	215				84	193			
Cumulative exposure (pack-years)										
Unexposed	297	778	1.00	Referent		181	327	1.00	Referent	
0.1–13.0	188	411	1.00	0.78–1.28		167	358	0.91	0.70–1.19	
13.1–23.0	36	83	0.89	0.57–1.39		35	78	0.83	0.52–1.30	
≥23.1	42	55	1.64	1.04–2.59	.09	42	55	1.54	0.97–2.44	.15
Missing values	87	215				84	193			

\*OR = odds ratio adjusted for age and sex–center interaction; CI = confidence interval.

†Two-tailed *P* value of test for linear trend.**Table 4.** Odds ratios of lung cancer from exposure to environmental tobacco smoke at the workplace

	All subjects*					Women*				
	Case subjects	Control subjects	OR	95% CI	<i>P</i> for trend†	Case subjects	Control subjects	OR	95% CI	<i>P</i> for trend†
Ever exposed										
No	276	687	1.00	Referent		240	535	1.00	Referent	
Yes	374	855	1.17	0.94–1.45		269	476	1.19	0.94–1.51	
Missing values	0	0				0	0			
Duration of exposure (in years)										
Unexposed	276	687	1.00	Referent		240	535	1.00	Referent	
1–29	278	634	1.15	0.91–1.44		211	399	1.14	0.89–1.47	
30–38	55	129	1.26	0.85–1.85		37	47	1.50	0.93–2.43	
≥39	39	91	1.19	0.76–1.86	.21	20	29	1.24	0.67–2.28	.10
Missing values	2	1				1	1			
Duration of exposure (level‡ × hours/day × years)										
Unexposed	276	687	1.00	Referent		240	535	1.00	Referent	
0.1–46.1	196	525	0.97	0.76–1.25		148	316	1.03	0.78–1.36	
46.2–88.9	47	105	1.41	0.93–2.12		26	54	1.08	0.65–1.81	
≥89.0	48	71	2.07	1.33–3.21	<.01	30	33	1.87	1.10–3.20	.03
Missing values	83	154				65	73			

\*OR = odds ratio adjusted for age and sex–center interaction; CI = confidence interval.

†Two-tailed *P* value of test for linear trend.

‡See text for details.

exposure. Statistically significant results were the reduced risk from childhood exposure and the increasing trend in risk for weighted duration of exposure to ETS from the spouse or at the workplace. Vehicles and public indoor settings did not represent an important source of ETS exposure. The analysis according to

time since last exposure suggested no increase in risk when a long time (i.e., ≥15 years) had elapsed since cessation of exposure.

An important aspect of our study in relation to previous studies is its size, which allowed us to obtain risk estimates with

**Table 5.** Odds ratios of lung cancer from combined exposure to environmental tobacco smoke from the spouse and at the workplace

	All subjects*					Women*				
	Case subjects	Control subjects	OR	95% CI	<i>P</i> for trend†	Case subjects	Control subjects	OR	95% CI	<i>P</i> for trend†
Ever exposed										
No	122	339	1.00	Referent		88	198	1.00	Referent	
Yes	527	1201	1.14	0.88–1.47		420	811	1.15	0.86–1.55	
Missing values	1	2				1	2			
Duration of exposure (in years)										
Unexposed	115	331	1.00	Referent		83	190	1.00	Referent	
1–36	362	876	1.11	0.85–1.46		282	573	1.09	0.80–1.50	
37–43	82	185	1.26	0.87–1.81		67	127	1.28	0.85–1.94	
≥44	70	125	1.29	0.87–1.92	.13	57	97	1.25	0.80–1.95	.19
Missing values	21	25				20	24			
Duration of exposure (hours/day × years)										
Unexposed	122	339	1.00	Referent		88	198	1.00	Referent	
0–165	289	749	0.91	0.69–1.20		214	483	0.87	0.63–1.21	
166–253	63	151	1.31	0.88–1.94		46	86	1.15	0.72–1.82	
≥254	57	101	1.46	0.96–2.22	.01	49	72	1.49	0.93–2.38	.03
Missing values	119	202				112	172			
Time since last exposure (in years)										
Unexposed	122	339	1.00	Referent		88	198	1.00	Referent	
≥16	121	327	0.92	0.67–1.26		99	235	0.92	0.64–1.33	
3–15	175	394	1.20	0.89–1.62		140	274	1.18	0.84–1.67	
0–2‡	211	459	1.18	0.88–1.59		162	282	1.22	0.87–1.72	
Missing values	21	23				20	22			

\*OR = odds ratio adjusted for age and sex–center interaction; CI = confidence interval.

†Two-tailed *P* value of test for linear trend.

‡Including current exposure.

good statistical precision, to separate sizable groups of case and control subjects with high exposure to ETS, and to conduct analyses after stratification for histologic type. However, our power calculation was based on an expected difference in risk from ETS exposure that was greater than that which we observed. Although we did not use an objective marker of past ETS exposure, we conducted a detailed assessment of exposure to ETS from various sources. In addition, we controlled for most potential confounders, and we validated the smoking status of the index subject and the spouse in a subgroup of case and control subjects.

The lack of full consistency of the results among the centers may limit the strength of our findings and the conclusions we can derive from them. However, we think that the combined dataset provides the most valid information on ETS-related risks. We based our conclusion on the following arguments: 1) We designed the study as a multicenter investigation and made efforts to acquire the same information from case and control subjects in the different centers; 2) although not fully consistent, the differences in the center-specific results were—in most cases—not statistically significant, and some random variability is inherent in comparisons between subgroups; 3) results were more consistent for variables that combined exposure to spousal and workplace ETS, which suggested that different degrees of misclassification in exposure contributed to center differences; and 4) we were not able to identify any obvious clustering of studies with different results related to aspects of design (e.g., centers with hospital-based control subjects and centers with community-based control subjects). The fact that the study was conducted in countries that use different languages might have also contributed to the heterogeneity of the results. The similar

size of the estimated effect of ETS exposure at the workplace, compared with ETS exposure from the spouse, is consistent with findings of a validation study (14) that we conducted among some 1300 women from 13 centers (including some centers participating in this study) that the workplace was the strongest predictor of urinary cotinine after smoking by the spouse.

We identified some potential methodologic problems in our study. Some aspects of the design of the study and, in particular, the criteria for selection of control subjects differed among centers. Although several authors consider hospital-based studies in general more prone to selection bias than community-based studies (21), the former studies may offer less opportunity for recall bias and, therefore, differential misclassification of exposure (21). We addressed this issue by comparing the results from subsets of centers defined according to their criteria for selection of control subjects, and we found only small differences. For example, the OR for ever spousal or workplace exposure was 1.12 (95% CI = 0.75–1.66) in centers with hospital-based control subjects and 1.13 (95% CI = 0.80–1.61) in centers with community-based control subjects.

The response rate differed among centers, but there was no relationship between the response rate and the log ORs of ever exposure to ETS during childhood (*P* values of linear regression for response rate: *P* = .23 in case subjects and *P* = .51 in control subjects), ever exposure to spousal ETS (*P* = .46 for case subjects and *P* = .80 for control subjects), or ever exposure to ETS at the workplace (*P* = .63 for case subjects and *P* = .71 for control subjects).

We did not require cytologic or histologic verification of lung cancer as a criterion for inclusion in the study; however, this information was available for more than 96% of the cases. Re-

**Table 6.** Odds ratios of lung cancer from combined exposure to environmental tobacco smoke from the spouse and at the workplace, by histologic type\*

	Histologic type			
	Adenocarcinoma	Squamous cell carcinoma	Small-cell carcinoma	Other types
Ever exposed				
N	267	92	56	95
OR	1.01	1.57	1.19	1.20
95% CI	0.73–1.40	0.89–2.76	0.62–2.30	0.70–2.04
Duration of exposure (in years)				
0.1–36.0				
N	190	59	33	69
OR	1.02	1.46	1.01	1.27
95% CI	0.72–1.44	0.79–2.67	0.49–2.06	0.72–2.23
36.1–43.0				
N	36	18	9	16
OR	0.95	2.15	1.57	1.40
95% CI	0.59–1.53	1.03–4.51	0.61–4.04	0.68–2.90
≥43.1				
N	33	13	13	8
OR	1.11	1.99	2.03	0.83
95% CI	0.67–1.86	0.88–4.52	0.84–4.90	0.34–2.04
<i>P</i> for trend†	.90	.03	.08	.84
Duration of exposure (hours/day × years)				
1–165				
N	147	49	29	56
OR	0.77	1.26	0.98	1.09
95% CI	0.54–1.10	0.68–2.32	0.48–2.02	0.62–1.94
166–253				
N	31	12	7	13
OR	1.10	1.88	1.46	1.49
95% CI	0.66–1.83	0.82–4.29	0.52–4.09	0.69–3.24
≥254				
N	30	11	6	8
OR	1.32	2.04	2.33	1.18
95% CI	0.77–2.25	0.85–4.89	0.77–7.10	0.48–2.93
<i>P</i> for trend†	.09	.06	.09	.46
Time since last exposure (in years)				
≥15.1				
N	64	23	12	16
OR	0.88	1.38	0.71	0.75
95% CI	0.53–1.32	0.70–2.74	0.31–1.65	0.37–1.52
2.1–15.0				
N	77	27	23	42
OR	0.94	1.53	1.45	1.59
95% CI	0.63–1.39	0.79–2.97	0.69–3.06	0.88–2.86
0.1–2.0				
N	113	39	19	34
OR	1.06	1.68	1.44	1.14
95% CI	0.73–1.54	0.50–3.16	0.65–3.19	0.62–2.11
<i>P</i> for trend†	.61	.11	.14	.25

\*N = number of exposed case subjects; OR = odds ratio adjusted for age and sex-center interaction; CI = confidence interval.

†Two-tailed *P* value of test for linear trend.

striction of the analysis to histologically verified cases had minor effects on the risk estimates: The OR for spousal or workplace exposure was 1.11 (95% CI = 0.86–1.43).

Misclassification of nonsmoking status of case and control subjects (i.e., confounding by active smoking) is an important potential source of bias in studies of lung cancer and ETS (1,22). We have three lines of evidence to address this issue.

First, we collected information on active smoking by case subjects and by control subjects, and, for inclusion in the study as a nonsmoker, we set a threshold of 400 cigarettes smoked during the entire life (i.e., about one cigarette per day for 1 year). Misclassification of smoking status is more likely to be present among such very light smokers than among nonsmokers. In our study, 164 case subjects and 438 control subjects (“occasional smokers”) reported ever consumption of fewer than 400 ciga-

rettes; their exclusion from the analysis had minor consequences on the results (OR for exposure to spousal ETS = 1.15; 95% CI = 0.86–1.54).

Second, in the urinary cotinine study mentioned above (14), 26 (1.9%) of 1369 women had cotinine levels above 100 ng/mg creatinine and were classified as potentially false-negative current smokers. Lee and Forey (23) discussed the effect of different factors that influence the magnitude of the possible bias from misclassification of smoking habits. If there is no true risk related to ETS exposure, a relative risk of the magnitude of that found in our study (i.e., 1.15) can be obtained assuming a misclassification rate of 2% (14), a proportion of smoking spouses of the order of 30%–50%, a proportion of smokers in the underlying population of 20%–40%, a concordance ratio of 3, and a relative risk of smoking in the order of 10–20. While the first



four assumptions may be reasonable, also in the context of our study, the magnitude of the effect of smoking is too high, since most misclassified subjects are light smokers or long-term quitters (24). A more realistic relative risk of smoking of 2 (24) would result in a relative risk due to misclassification of the order of 1.01–1.02, all other assumptions being equal. In addition, we conducted a validation study based on cross-interviews; for 408 subjects enrolled in three centers, of whom 50 were not included in this analysis, a next of kin—mainly the spouse—completed a short questionnaire aimed at validating the non-smoking status of the index subject (25). Misclassification on never-smoking status in this sample was 1.2%, based on one of 175 case subjects and four of 233 control subjects, none of whom was classified as a current smoker. It is thus unlikely that the inclusion of smokers misclassified as nonsmokers affected our results.

Misclassification of exposure to ETS is another important potential source of bias (1,22). In the urinary cotinine study, we found a good correlation between reported exposure to ETS and cotinine level (14); however, this study could validate only the recent history of exposure. The results of the analysis of the interviews with relatives on ETS exposure conducted on a subgroup of 213 case and control subjects from one center in this study (25) showed a very good correlation between the smoking status and the cumulative consumption by the spouse and the information reported by the study subjects (Spearman correlation coefficient = .92), without a difference between case and control subjects. Finally, differential misclassification of exposure (i.e., case subjects overreporting ETS exposure as compared with control subjects), if present in our study, would hardly explain the lack of a positive association with childhood exposure. If differential misclassification of ETS exposure is unlikely, nondifferential misclassification (resulting in decreased risk estimates in dichotomous variables and in the highest category of categorical quantitative variables) is a plausible source of bias in our study, as a result of imperfect measures of all dimensions of ETS exposure.

An important potential problem in studies on ETS and lung cancer is the lack of proper control for potential confounders other than active smoking. Authors have presented some evidence on differences in habits other than smoking in households with and without smokers (26,27). In particular, Whichelow et al. (28) addressed this issue in a European population and reported a healthier diet by nonsmokers than by smokers in the U.K. We found no evidence that other known or suspected risk factors of lung cancer and their correlates, such as educational level used as a proxy for socioeconomic status, occupational exposure to carcinogens, residence in urban areas, and low consumption of vegetables, explained the risks from ETS exposure either from the spouse or at the workplace. In particular, no association was present among control subjects between smoking status of the spouse and consumption of vegetables, green vegetables, and fruits and amount of intake of  $\beta$ -carotene.

We conducted an analysis based on logistic regression models that used the whole dataset, after controlling for the study center. An alternative approach would have been to analyze each center separately and to combine the center-specific risk estimates by use of a random effects model, as is done in meta-analyses (29). Although we do not favor this latter approach,

since our study was conducted by use of the same methodology in the different centers, the meta-analysis approach leads to very similar results, although with wider CIs; e.g., the OR of ever exposure to spousal ETS was 1.13 (95% CI = 0.87–1.47), the OR of ever exposure to ETS at the workplace was 1.14 (95% CI = 0.87–1.49), and the ORs of duration (in hours/day  $\times$  years) of exposure to spousal or workplace ETS were 0.87 (95% CI = 0.65–1.18), 1.34 (95% CI = 0.74–2.42), and 1.48 (95% CI = 0.87–2.49) for the three categories shown in Table 5.

The available literature on ETS exposure from the spouse and lung cancer is large [reviewed in (1–4)]. However, only six studies are available from Europe; two of them, conducted in Greece (5,10), showed a twofold increase in risk for women ever married to a smoker. Of the other studies, one from Scotland (7) provided very unstable risk estimates of the same magnitude as the Greek studies and two—one from the U.K. (6) and the other from Sweden (9)—provided little evidence of an association. The last study, also from Sweden (8), was the only one that presented results solely by level of exposure and showed no excess risk below exposure to ETS from 15 cigarettes per day or for 30 years and a threefold excess above these exposure levels. Pershagen (30) combined the six studies and estimated an overall relative risk of 1.47 (95% CI = 1.12–1.92), whereas the U.S. Environmental Protection Agency (EPA) (3) excluded the Greek studies and calculated a combined relative risk of 1.17 (90% CI = 0.84–1.62). Our summary OR is compatible with the EPA estimate.

The fact that most subjects in our study reported having ended their ETS exposure from the spouse or at the workplace several years before the interview may help to explain why the overall risk estimate for ever spousal smoking was somewhat lower in this study than in previous investigations, such as the studies from Greece (5,10) that were conducted in a population in which most subjects classified as exposed to spousal ETS were currently exposed. Results obtained from studies in the United States (31,32) also suggest a decrease in the risk from ever spousal (or “home”) ETS exposure compared with previous reports [see (3,30) for a review].

The evidence from the available European studies of an association between ETS exposure during childhood and lung cancer risk is inconsistent (8,9). Among the non-European studies, Janerich et al. (33) provided evidence of an increased risk related to exposure in childhood or adolescence. The remaining studies [see (34) for a review], however, failed to confirm this finding. In the light of the inconsistent findings of other studies, our results on childhood ETS exposure can be plausibly interpreted as sampling fluctuation around a relative risk of 1 (no effect) and do not allow us to conclude that ETS exposure during childhood is protective against lung cancer.

Our results on the effect of ETS exposure at the workplace parallel those of a large U.S. study (31) in showing a risk similar to that of spousal exposure to ETS and a dose–response relationship. The evidence on workplace exposure to ETS from other studies, in particular from other European studies, is not consistent [see (30) for a review]. A few studies have reported results on ETS exposure in public indoor settings; in particular, two studies (6,35) showed no clear pattern of risk, whereas a large U.S. study (31) reported an increased risk for exposure in

social settings and a positive relationship with duration of exposure.

The higher risk found for both spousal and workplace exposures to ETS for squamous cell carcinoma and small-cell carcinoma, compared with adenocarcinoma, was not statistically significant but was consistent with the results of studies on ETS conducted both in Europe (8,10) and—for spousal ETS exposure—in the United States (31). However, the small size of particles in ETS would be consistent with a carcinogenic effect in the distant part of the lung, where adenocarcinoma preferentially occurs. It should also be noted that, in studies conducted in China (36,37), a higher risk was found of adenocarcinoma compared with other histologic types.

When taken together, our results on exposure to ETS during adulthood are in agreement with the available evidence and, in particular, with large studies from the United States (31,32). We think that minor discrepancies between the two studies, such as a somewhat stronger effect of spousal smoking in the U.S. studies and the lack of an effect of “social” sources in our study, reflect differences in smoking patterns between the European and U.S. populations. The comparison between our results and those of other studies conducted in Europe is hampered by the limited amount of information available from the latter.

In conclusion, our study provides the most precise available estimate of the effect of ETS on lung cancer risk in western European populations. We found no increased risk for childhood exposure, a result consistent with most of the available data. The risk from ever exposure to spousal ETS was consistent with the combined available evidence from European studies, but it was lower than some previous estimates—a result that could be explained by the large number of subjects whose exposure to ETS ended several years earlier. The lack of reported results on the effect of cessation of ETS exposure in previous European studies does not enable us to explore this explanation. There was also a nonsignificant dose–response relationship with duration of exposure. We also found an association of similar strength with workplace exposure. Dose–response relationships were more consistent and risks were higher, although in most cases they were not statistically significant, with combined indicators of spousal and workplace ETS exposure.

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## NOTES

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