Environmental Tobacco Smoke and Lung Cancer in Nonsmoking Women

A Multicenter Study

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Objective.—To determine the relative risk (RR) of lung cancer in lifetime never smokers associated with environmental tobacco smoke (ETS) exposure.

Design.—Multicenter population-based case-control study.

Setting.—Five metropolitan areas in the United States: Atlanta, Ga, Houston, Tex, Los Angeles, Calif, New Orleans, La, and the San Francisco Bay Area, Calif.

Patients or Other Participants.—Female lifetime never smokers: 653 cases with histologically confirmed lung cancer and 1253 controls selected by random digit dialing and random sampling from the Health Care Financing Administration files for women aged 65 years and older.

Main Outcome Measure.—The RR of lung cancer, estimated by adjusted odds ratio (OR) with 95% confidence interval (CI), associated with ETS exposure.

Results.—Tobacco use by spouse(s) was associated with a 30% excess risk of lung cancer: all types of primary lung carcinoma (adjusted OR=1.29; $P<.05$), pulmonary adenocarcinoma (adjusted OR=1.28; $P<.05$), and other primary carcinomas of the lung (adjusted OR=1.37; $P=.18$). An increasing RR of lung cancer was observed with increasing pack-years of spousal ETS exposure (trend $P=.03$), such that an 80% excess risk of lung cancer was observed for subjects with 80 or more pack-years of exposure from a spouse (adjusted OR=1.79; 95% CI=0.99 to 3.25). The excess risk of lung cancer among women ever exposed to ETS during adult life in the household was 24%; in the workplace, 39%; and in social settings, 50%. When these sources were considered jointly, an increasing risk of lung cancer with increasing duration of exposure was observed (trend $P=.001$). At the highest level of exposure, there was a 75% increased risk. No significant association was found between exposure during childhood to household ETS exposure from mother, father, or other household members; however, women who were exposed during childhood had higher RRs associated with adult-life ETS exposures than women with no childhood exposure. At the highest level of adult smoke-years of exposure, the ORs for women with and without childhood exposures were 3.25 (95% CI, 2.42 to 7.46) and 1.77 (95% CI, 0.98 to 3.19), respectively.

Conclusion.—Exposure to ETS during adult life increases risk of lung cancer in lifetime nonsmokers.

(*JAMA.* 1994;271:1752-1759)

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IN JANUARY 1993, the US Environmental Protection Agency (EPA) issued a report on the respiratory health effects of passive smoking in which it concluded that environmental tobacco smoke (ETS) is a human lung carcinogen, responsible for approximately 3000 lung cancer deaths per year in US nonsmokers.[1] A total of 30 epidemiologic studies conducted worldwide were included in the EPA risk assessment, including 11 studies conducted in the United States.[2-31] Of the US studies, the report of findings from the first 3 years of this multicenter study[2] contributed the greatest individual study weight to the US summary relative risk (RR) estimates for lung cancer: 1.19 (95% confidence interval [CI], 1.04 to 1.35) associated with "ever exposed" to spousal ETS and 1.38 (95% CI, 1.13 to 1.70) for the highest level of spousal ETS exposure. The weight accorded this study in the EPA report reflected the large number of lifetime nonsmokers with lung cancer (n=420), as well as the study design used in this case-control study. This study was designed specifically to evaluate the role of ETS exposure in the etiology of lung cancer in lifetime nonsmokers.

Two large US studies have been published since the preparation of the EPA report.[32,33] Because these studies are similar in size and scope to our first report, their findings would have had a similar impact on the summary US risk estimates. Brownson et al[32] observed no increased risk in the ever-exposed category for spousal ETS (adjusted odds ratio [OR]=1.0; 95% CI, 0.8 to 1.2); however, the CI includes 1.19, the US summary point estimate. The highest exposure category (greater than 40 pack-years) in the study by Brownson et al yielded an RR estimate of 1.3 (95% CI, 1.0 to 1.7), quite similar to the US "high-exposure" summary estimate of 1.38. In the second study by Stockwell et al,[33] the RR estimates are among the highest reported for US studies: 1.6 (95% CI, 0.8 to 3.0) for ever exposed and 2.4 (95% CI, 1.1 to 5.3) for 40 or more smoke-years in adulthood.

This report extends the findings of this multicenter study on completion of 2 additional years of subject accrual.

METHODS

The methods and procedures followed in this study have been previously described in detail.[2] The study was a population-based case-control study of lung cancer in women who have never used any tobacco product. Eligible cases included microscopically confirmed primary carcinoma of the lung (*International Classification of Diseases, Ninth Revision* [*ICD-9*], code 162) that were diagnosed between December 1, 1986, and November 30, 1988, among female residents of metropolitan Atlanta, Ga (Clayton, Cobb, DeKalb, Fulton, and Gwinnett counties), and Houston, Tex (Galveston and Harris counties), and during 2 additional years, 1989 and 1990, among residents of New Orleans, La (Jefferson, Orleans, and St Bernard parishes), Los Angeles, Calif (Los Angeles County), and the San Francisco Bay Area, Calif (Alameda, Contra Costa, Marin, San Francisco, San Mateo, and Santa Clara counties). Additional eligibility criteria included age at diagnosis (20 to 79 years), language (English, Spanish, or Chinese), history of previous cancer (none), and lifetime tobacco use (fewer than 100 cigarettes smoked and no use of any other form of tobacco for more than 6 months). This project was approved by all appropriate institutional review boards.

A population-based control group was selected by random digit dialing and supplemented by random sampling from the Health Care Financing Administration files for women 65 years and older. Controls were frequency matched to cases on race and age (younger than 50 years, 50 to 59 years, 60 to 69 years, and 70 to 79 years) in a 2:1 ratio of controls to cases and met the same residence, language, and tobacco use criteria as cases. The population control group was selected as the primary comparison group in case-control analyses. A second control group was selected during the first 3 years of the study (December 1, 1985, to November 30, 1988) from women aged 20 to 79 years with a diagnosis of primary carcinoma of the colon (*ICD-9*, code 153) who met the same residence, language, and tobacco use criteria as cases and were frequency matched to the case series by 10-year age group and race. This control group was selected as a means of assessing recall or response bias associated with a recent diagnosis of cancer or with being ill. In the report based on the first 3 years of case accrual, the results were consistent for case-control comparisons using each control group.[2] This component of the study was not extended into the final 2 years.

Lifetime smoking status was determined in a three-tiered approach. Information was obtained on each potential study subject's personal use of tobacco, first from the medical record of the cancer cases, then from the patient's personal physician, and finally from the potential study subject or her next of kin for those patients whose medical records and physicians did not indicate a history of smoking. The telephone screening procedure (tier 3) was also used to determine lifetime tobacco use of the population control group. At the interview, the tobacco use screening questions were repeated to confirm each study subject's reported status as a lifetime nonuser of tobacco.

Of the 17 447 potential cases ascertained in the five study centers, 800 were found to meet all eligibility criteria. In-person interviews were completed for 665 (83%) of 800 incident cases and 1278 (70%) of 1826 population controls. An interview was solicited from the next of kin of cases who were deceased or were too ill to participate in an interview. Information for 241 lung cancer cases (36%) was obtained from next-of-kin respondents.

At interview, a urine sample was collected from all consenting study subjects who were able to provide such a sample. Urinary cotinine and creatinine were determined and the ratio used as an indicator of current smoking status. The request for the sample was not made until the interview. Specimens were stored at −20°C until analysis at the American Health Foundation, Valhalla, NY.

Cotinine was quantitated by radioimmunoassay using the method of Haley et al[34] with a modification of the antibody of Langone et al.[35] Cotinine concentrations were adjusted for urine flow based on creatinine values by determining the nanograms of cotinine per milligrams of creatinine. Creatinine was determined by spectrophotometry using the Kodak Ektachem 400 Clinical Chemistry Analyzer (Kodak, Rochester, NY).

Urine samples were analyzed for 356 (53.5%) of 665 cases and 1064 (83.3%) of 1278 controls. The difference in the proportions of cases and controls is attributable to deceased cases. A high proportion of living study subjects were able and willing to provide a urine sample, and the proportions were similar for cases (81.1%) and controls (83.3%) despite differences in health status. As in the original report, subjects in the case and control groups whose cotinine/creatinine concentration exceeded 100 ng/mg were excluded from the study to eliminate persons likely to be active smokers.[2] Two (0.6%) of 356 cases and 25 (2.3%) of 1064 controls had cotinine/creatinine concentrations of 100 ng/mg or higher. Although no optimum concentration has been established as a cut point for distinguishing true nonsmokers from smokers in studies that are restricted to women and include subjects with cancer, a concentration of 50 ng/mg or lower has been used as the eligibility criterion in a large study of healthy, free-living subjects,[36] and others have been suggested.[37,38] In high-exposure settings, urinary cotinine in nonsmokers has reached a concentration of 55 ng/mg of cotinine/creatinine.[39,40] In this study, nine cases (2.5%) and 29 controls (2.7%) had urinary concentrations of 55 to 99 ng/mg. Analyses of ETS-related risk estimates were also conducted using a cut point of 55 ng/mg of cotinine/creatinine as an exclusion criterion to evaluate the possibility that the study findings were biased as a result of inclusion of study subjects with borderline concentrations (55 to 99 ng/mg) of cotinine/creatinine.

Representative diagnostic specimen slides for each case were requested from the hospital for review by one pathologist specializing in pulmonary pathology. A total of 562 (85%) of 663 potential cases had diagnostic material available for review, and 552 (98%) of the reviewed cases were confirmed as primary bronchogenic carcinoma. After exclusion of the 10 cases that had review diagnoses inconsistent with primary bronchogenic carcinoma, the final interviewed case series included 653 lung cancer cases: 497 adenocarcinomas (76.1%); 74 large-cell carcinomas (11.3%); 40 squamous cell carcinomas (6.1%); 24 small-cell carcinomas (3.7%); and 18 other primary lung carcinomas (2.8%). The 101 cases with diagnostic slides that were unavailable for review were classified according to the original hospital and tumor registry diagnosis. The distribution by cell type was similar for the reviewed and nonreviewed cases except for a higher proportion of cases in the "other primary lung carcinomas" category among nonreviewed cases. Analyses of ETS-related risk estimates were also conducted excluding cases that did not undergo independent review to evaluate consistency of the findings.

In-person interviews followed an extensive structured questionnaire designed to obtain information on household, occupational, and other exposures to ETS during each study subject's lifetime, as well as other exposures associated with lung cancer. Exposure to ETS was examined by source during childhood (father, mother, and other household members who lived in the home for at least 6 months) and during adult life (spouse, other household members, occupational, and social exposures). Childhood included the years from birth through age 18 years. Exposures from parents after that time were classified as other household members during adult life. Dichotomous ETS exposure (ever or never) was examined by source and type of tobacco. Pack-years of cigarette smoke exposure from spouse were calculated by multiplying the number of packs smoked per day by the number of years the spouse smoked cigarettes while living with the study subject. Duration of exposure by source was measured in years. Years of exposure in occupational settings represent the sum of years of employment in each job in which persons were reported to have smoked around the study subject. Years of exposure from individual sources were examined, and a summary measure (smoke-years) of exposure during childhood and adult life was calculated. Smoke-years

Table 1.—Distribution of Lung Cancer Cases and Controls According to Selected Demographic Characteristics

Characteristic	Lung Cancer Cases, No. (%)	Population Controls, No. (%)
Study center		
Atlanta, Ga	46 (7.0)	76 (6.1)
Houston, Tex	41 (6.3)	42 (3.4)
Los Angeles, Calif	264 (40.4)	512 (40.9)
New Orleans, La	34 (5.2)	57 (4.5)
San Francisco Bay Area, Calif	268 (41.0)	566 (45.2)
Respondent		
Study subject	412 (63.1)	1253 (100.0)
Next of kin	241 (36.9)	...
Age, y		
<50	70 (10.7)	165 (13.1)
50-59	110 (16.9)	154 (12.3)
60-69	213 (32.6)	398 (31.8)
70-79	260 (39.8)	536 (42.8)
Race/ethnic group		
White	382 (58.5)	765 (61.1)
Black	60 (9.2)	171 (13.7)
Hispanic	68 (10.4)	99 (7.9)
Asian	125 (19.1)	184 (14.7)
Other	17 (2.6)	23 (1.8)
Unknown or refused to answer	1 (0.2)	11 (0.9)
Annual income, $		
<8000	103 (15.8)	144 (11.5)
8000-12 999	88 (13.5)	162 (12.9)
13 000-19 999	84 (12.9)	168 (13.4)
20 000-34 999	114 (17.5)	250 (19.9)
35 000-49 999	63 (9.7)	136 (10.9)
≥50 000	94 (14.4)	216 (17.2)
Unknown or refused to answer	107 (16.4)	177 (14.1)
Education		
<High school	216 (33.1)	266 (21.2)
High school	217 (33.2)	393 (31.4)
Some college	99 (15.2)	315 (25.1)
College	62 (9.5)	154 (12.3)
Graduate	46 (7.0)	116 (9.3)
Unknown	13 (2.0)	9 (0.7)

represent the sum of reported years of exposure to ETS from each individual source in childhood (father, mother, and other household members) or in adult life (spouse, other household members, occupational, and social). The variable does not represent years per se because these exposures may occur concurrently.

All lung cancer cases combined were compared with the controls, as were cases of adenocarcinoma of the lung (76.1% of the total cases) and other histological types combined (squamous cell carcinoma, small-cell carcinoma, large-cell carcinoma, and other types, 23.9% of the total cases). In addition, analyses restricted to self-respondents were compared with those that also included proxy respondents.

Unconditional logistic regression analyses were used to estimate the associations by summary adjusted ORs, 95% CIs, and test statistics.[41,42] The ORs were adjusted for design or sampling variables (age, race, and study center), as well as education, family history of lung cancer, employment in potentially high-risk occupations for 5 or more years (production jobs in painting, mining, textile, insulation, shipyard, cement, roofing, smelting, radiation, petroleum, hairdressing, and printing industries), dietary cholesterol intake, and an index of dietary antioxidant consumption based on weekly consumption of fruits and vegetables and supplemental vitamin use at least four times per week. No significant interactions were observed. Previous lung disease and dietary beta carotene, vitamin C, and vitamin E were also evaluated, but were not included in the final models because they did not confound the ETS findings and did not contribute further to the association between ETS and lung cancer.

Table 2.—Association Between Smoking Status of Spouse and Lung Cancer Risk in Nonsmoking Women*

Spouse Ever Smoked Tobacco, by Type	Cases, No. Exposed/ No. of Cases†	Controls, No. Exposed/ No. of Controls	Crude OR (95% CI)	Adjusted OR (95% CI)
All lung carcinomas				
Any type of tobacco	433/651	766/1253	1.26 (1.04-1.54)†	1.29 (1.04-1.60)†
Cigarettes	386/648	691/1253	1.20 (0.99-1.45)	1.18 (0.96-1.46)
Cigars	85/641	138/1253	1.24 (0.93-1.65)	1.25 (0.92-1.71)
Pipes	86/640	158/1253	1.08 (0.81-1.43)	1.19 (0.88-1.60)
Adenocarcinoma				
Any type of tobacco	334/496	766/1253	1.31 (1.05-1.63)†	1.28 (1.01-1.62)†
Cigarettes	298/493	691/1253	1.24 (1.01-1.54)†	1.18 (0.94-1.49)
Cigars	58/489	138/1253	1.09 (0.79-1.51)	1.08 (0.76-1.53)
Pipes	62/488	158/1253	1.01 (0.74-1.38)	1.04 (0.75-1.46)
Other histological types				
Any type of tobacco	99/155	766/1253	1.12 (0.80-1.59)	1.37 (0.92-2.03)
Cigarettes	88/155	691/1253	1.07 (0.76-1.50)	1.20 (0.83-1.75)
Cigars	27/152	138/1253	1.75 (1.11-2.74)	1.88 (1.14-3.08)†
Pipes	24/152	158/1253	1.30 (0.82-2.07)	1.79 (1.08-2.95)†

*Adjusted for age; race (white, black, Asian, and Hispanic or other); study area (Los Angeles, Calif, San Francisco Bay Area, Calif, South); education (less than high school, high school graduate, some college or more); fruits, vegetables, and supplemental vitamin index; dietary cholesterol; family history of lung cancer; and employment in high-risk occupations. OR indicates odds ratio; CI, confidence interval.
†The number of cases and controls with responses to each question.
‡$P<.05$.

Table 3.—Association Between Risk of Lung Cancer and Pack-Years of Environmental Tobacco Smoke Exposure From Spouse(s) Among Nonsmoking Women*

Pack-Years of Exposure	Cases	Controls	Crude OR (95% CI)	Adjusted OR (95% CI)
All lung carcinomas				
0	267	562	1.00 ...	1.00 ...
≤15.0	146	300	1.02 (0.80-1.31)	1.08 (0.83-1.39)
15.1-39.9	92	190	1.02 (0.76-1.36)	1.04 (0.76-1.42)
40.0-79.9	80	126	1.34 (0.98-1.83)	1.36 (0.97-1.91)
≥80.0	24	27	1.87 (1.06-3.31)†	1.79 (0.99-3.25)
			Trend P=.03	Trend P=.03
Adenocarcinoma				
0	199	562	1.00 ...	1.00 ...
≤15.0	109	300	1.03 (0.78-1.35)	1.06 (0.80-1.40)
15.1-39.9	70	190	1.04 (0.76-1.43)	1.02 (0.72-1.42)
40.0-79.9	65	126	1.46 (1.04-2.05)†	1.41 (0.98-2.03)
≥80.0	18	27	1.88 (1.02-3.49)†	1.73 (0.91-3.31)
			Trend P=.01	Trend P=.05
Other histological types				
0	68	562	1.00 ...	1.00 ...
≤15.0	37	300	1.02 (0.67-1.56)	1.18 (0.75-1.87)
15.1-39.9	22	190	0.96 (0.58-1.59)	1.12 (0.64-1.96)
40.0-79.9	15	126	0.98 (0.55-1.78)	1.16 (0.62-2.19)
≥80.0	6	27	1.84 (0.73-4.61)	1.97 (0.75-5.19)
			Trend P=.64	Trend P=.29

*Adjusted for age; race; study area; education; fruits, vegetables, and supplemental vitamin index; dietary cholesterol; family history of lung cancer; and employment in high-risk occupations. OR indicates odds ratio; CI, confidence interval.
†$P<.05$.

RESULTS

The distribution of cases and controls by study center, respondent status, age, racial/ethnic group, annual household income, and highest level of education completed is shown in Table 1. Approximately 40% of the lung cancer cases and controls were residents of Los Angeles and a similar proportion were from the San Francisco Bay Area, the two largest study centers in which case and population control ascertainment encompassed a 5-year period. The three smaller study centers in the southern United States (Atlanta, Houston, and New Orleans) contributed the remaining study subjects.

The case-control series had a relatively large proportion of cases aged 60 to 79 years (72%) with a similar proportion of controls in this age group. As noted previously,[2] the age distribution in this series of female lifetime never smokers with lung cancer is older than all female lung cancer cases in the Surveillance, Epidemiology, and End Results (SEER) Program, 1973 through 1988.[43]

The largest proportions of lung cancer cases (58.5%) and controls (61.1%) were white. A larger proportion of cases were self-identified as Asian American and Hispanic and a smaller proportion as African American (blacks) compared with controls. Approximately 42% of cases and 38% of controls reported an annual household income of less than $20 000 per year. Compared with controls, lung cancer cases tended to have a lower level of education: 66.3% of cases and 52.6% of controls had no more than a high school education.

Table 2 displays the estimated RRs of lung cancer associated with ever living with a spouse who smoked by type of tobacco. A 30% excess risk associated with tobacco use by spouse(s) was observed for all histopathologic types of lung cancer combined (adjusted OR=1.29; $P<.05$), for adenocarcinoma of the lung (adjusted OR=1.28; $P<.05$), and for primary lung carcinomas other than adenocarcinoma (adjusted OR=1.37; $P=.18$). The only individual types of tobacco associated with significantly elevated risks of lung cancer are cigar- and pipe-smoke exposure for bronchogenic carcinomas other than adenocarcinoma: cigars, adjusted OR=1.88 and $P=.01$; pipe, adjusted OR=1.79 and $P=.02$.

The estimated RRs of lung cancer associated with pack-years of exposure to spousal ETS are presented in Table 3. Increasing risk of lung cancer with increasing pack-years of spousal ETS exposure is observed for all lung carcinomas combined and for the two histopathologic subgroups. The risk estimates are similar within the histopathologic subgroups; however, the trend is significant only for all lung cancers combined ($P=.03$) and pulmonary adenocarcinoma ($P<.05$). When the analysis was restricted to self-respondents only, similar estimates of risk of lung cancer were observed with a trend of increasing risk of lung cancer at increasing levels of exposure ($P=.03$).

Exposure to ETS during childhood and adult life from multiple sources was evaluated. The risks of lung cancer associated with household ETS exposures during childhood as a result of father, mother, or other household member smoking are shown in Table 4. None of the RR estimates significantly differs from unity. The association of cumulative years of household exposure to ETS during childhood with lung cancer risk was evaluated (Table 5). No increased risk was associated with increasing duration of smoke exposure during childhood. Childhood smoke-years were unknown for a large proportion (20%) of the interviews with proxy respondents and for 5% of the interviews conducted with the study subject. For those interviews with data available to calculate smoke-years, 54% of proxy respondent interviews vs 38% of direct study subject interviews reported no exposure during childhood. The data presented, therefore, are for analyses restricted to self-respondents. No differences were observed by pathology review status; dietary cholesterol intake; level of the fruits, vegetables, and supplemental vitamin use index; age group; or educational attainment. Black study subjects had a twofold elevation in risk in the highest exposure category, and Asians showed twofold reduction in risk at this level; however, these two point estimates did not significantly differ. Restricting years of ETS exposure during childhood to those from the mother yielded similar nonsignificant trends.

Table 4.—Association Between Risk of Lung Cancer and Childhood Exposure to Tobacco Smoke Among Nonsmoking Women*

Ever Smoked Tobacco	Cases, No. Exposed/ No. of Cases	Controls, No. Exposed/ No. of Controls	Crude OR (95% CI)	Adjusted OR (95% CI)
All lung carcinomas				
Father	304/603	669/1225	0.85 (0.70-1.03)	0.83 (0.67-1.02)
Mother	76/624	161/1240	0.93 (0.69-1.24)	0.86 (0.62-1.18)
Other household members	131/617	269/1253	0.99 (0.78-1.25)	1.03 (0.80-1.32)
Any household member	377/606	808/1238	0.88 (0.72-1.07)	0.89 (0.72-1.10)
Adenocarcinoma				
Father	238/466	669/1225	0.87 (0.70-1.07)	0.82 (0.66-1.04)
Mother	60/480	161/1240	0.96 (0.70-1.32)	0.92 (0.65-1.29)
Other household members	98/471	269/1253	0.96 (0.74-1.25)	0.99 (0.75-1.30)
Any household member	290/469	808/1238	0.86 (0.69-1.07)	0.85 (0.68-1.08)
Other histological types				
Father	66/137	669/1225	0.77 (0.54-1.10)	0.82 (0.56-1.20)
Mother	16/144	161/1240	0.84 (0.49-1.45)	0.61 (0.32-1.16)
Other household members	33/146	269/1253	1.07 (0.71-1.61)	1.19 (0.77-1.85)
Any household member	87/137	808/1238	0.93 (0.64-1.34)	1.01 (0.68-1.51)

*Adjusted for age; race; study area; education; fruits, vegetables, and supplemental vitamin index; dietary cholesterol; family history of lung cancer; and employment in high-risk occupations. OR indicates odds ratio; CI, confidence interval.

Table 5.—Association Between Risk of Lung Cancer and Childhood Smoke-Years of Exposure Among Nonsmoking Women (Self-respondents Only)*

Childhood Smoke-Years of Household Exposure	Cases	Controls	Crude OR (95% CI)	Adjusted OR (95% CI)
All lung carcinomas				
0	148	444	1.00 ...	1.00 ...
1-17	95	291	0.98 (0.73-1.32)	0.99 (0.73-1.35)
≥18	146	485	0.90 (0.70-1.17)	0.88 (0.67-1.16)
			Trend P=.58	Trend P=.36
Adenocarcinoma				
0	120	444	1.00 ...	1.00 ...
1-17	73	291	0.93 (0.67-1.29)	0.92 (0.65-1.29)
≥18	123	485	0.94 (0.71-1.25)	0.89 (0.66-1.19)
			Trend P=.66	Trend P=.43
Other histological types				
0	28	444	1.00 ...	1.00 ...
1-17	22	291	1.20 (0.67-2.14)	1.32 (0.72-2.41)
≥18	23	485	0.75 (0.43-1.33)	0.85 (0.47-1.54)
			Trend P=.33	Trend P=.58

*Adjusted for age; race; study area; education; fruits, vegetables, and supplemental vitamin index; dietary cholesterol; family history of lung cancer; and employment in high-risk occupations. OR indicates odds ratio; CI, confidence interval.

Table 6 presents the estimated RRs associated with adult ETS exposure (ever exposed and years of exposure by individual sources during adult life). Elevations in risk are associated with increasing duration of exposure at home (trend $P=.11$), on the job (trend $P=.001$), and in social settings (trend $P=.002$). The increased risk of lung cancer among women ever exposed to ETS during adult life in the household is 24%; in occupational settings, 39%; and in social settings, 50%. The pattern of response is similar in the two histologic subgroups; however, the tests of trend are statistically significant only in the largest subgroup, pulmonary adenocarcinoma.

As shown in Table 7, when all sources of exposure to ETS during adult life are

Table 6.—Association Between Risk of Lung Cancer and Adult Exposures to Cigarette Smoke Among Nonsmoking Women*

Exposure by Source, y	Cases, No. Exposed/ No. of Cases	Controls, No. Exposed/ No. of Controls	Crude OR (95% CI)	Adjusted OR (95% CI)
All Lung Carcinomas				
Household exposure (spouse and other)				
Ever exposed	509/653	941/1253	1.17 (0.94-1.47)	1.23 (0.96-1.57)
0	153	321	1.00 ...	1.00 ...
1-15	184	393	0.98 (0.76-1.27)	1.10 (0.83-1.46)
16-30	143	244	1.23 (0.93-1.63)	1.33 (0.98-1.80)
>30	173	295	1.23 (0.94-1.61)	1.23 (0.91-1.66)
			Trend P=.05	Trend P=.11
Adenocarcinoma				
Ever exposed	389/497	941/1253	1.19 (0.93-1.53)	1.16 (0.89-1.52)
0	115	321	1.00 ...	1.00 ...
1-15	139	393	0.99 (0.74-1.32)	1.04 (0.77-1.42)
16-30	108	244	1.24 (0.91-1.69)	1.26 (0.90-1.76)
>30	135	295	1.28 (0.95-1.72)	1.20 (0.87-1.66)
			Trend P=.04	Trend P=.17
Other Histological Types				
Ever exposed	120/156	941/1253	1.11 (0.75-1.64)	1.51 (0.95-2.39)
0	38	321	1.00 ...	1.00 ...
1-15	45	393	0.97 (0.61-1.53)	1.39 (0.83-2.32)
16-30	35	244	1.21 (0.74-1.98)	1.59 (0.92-2.77)
>30	38	295	1.09 (0.68-1.75)	1.31 (0.76-2.26)
			Trend P=.53	Trend P=.32
All Lung Carcinomas				
Occupational exposure				
Ever exposed	385/609	756/1247	1.12 (0.91-1.36)	1.39 (1.11-1.74)‡
0	224	491	1.00 ...	1.00 ...
1-15	213	450	1.04 (0.83-1.30)	1.30 (1.01-1.67)†
16-30	118	223	1.16 (0.88-1.53)	1.40 (1.04-1.88)†
>30	54	83	1.43 (0.98-2.08)	1.86 (1.24-2.78)‡
			Trend P=.06	Trend P=.001
Adenocarcinoma				
Ever exposed	300/465	756/1247	1.18 (0.95-1.47)	1.46 (1.14-1.86)‡
0	165	491	1.00 ...	1.00 ...
1-15	167	450	1.10 (0.86-1.42)	1.35 (1.02-1.79)†
16-30	93	223	1.24 (0.92-1.67)	1.49 (1.08-2.05)†
>30	40	83	1.43 (0.95-2.18)	1.87 (1.19-2.92)‡
			Trend P=.05	Trend P=.001
Other Histological Types				
Ever exposed	85/144	756/1247	0.94 (0.66-1.33)	1.26 (0.85-1.88)
0	59	491	1.00 ...	1.00 ...
1-15	46	450	0.85 (0.57-1.28)	1.15 (0.73-1.82)
16-30	25	223	0.93 (0.57-1.53)	1.18 (0.68-2.04)
>30	14	83	1.40 (0.75-2.63)	2.00 (1.02-3.90)†
			Trend P=.62	Trend P=.09
All Lung Carcinomas				
Social exposure¶				
Ever exposed	189/615	297/1244	1.42 (1.14-1.75)‡	1.50 (1.19-1.89)§
0	426	947	1.00 ...	1.00 ...
1-15	110	177	1.38 (1.06-1.80)†	1.45 (1.09-1.92)†
16-30	48	68	1.57 (1.07-2.31)†	1.59 (1.06-2.40)†
>30	31	52	1.33 (0.84-2.10)	1.54 (0.93-2.53)
			Trend P=.006	Trend P=.002
Adenocarcinoma				
Ever exposed	147/469	297/1244	1.46 (1.15-1.84)‡	1.53 (1.19-1.97)‡
0	322	947	1.00 ...	1.00 ...
1-15	84	177	1.40 (1.05-1.86)†	1.45 (1.07-1.97)†
16-30	41	68	1.77 (1.18-2.67)‡	1.81 (1.18-2.77)‡
>30	22	52	1.24 (0.74-2.08)	1.45 (0.83-2.53)
			Trend P=.006	Trend P=.002
Other Histological Types				
Ever exposed	42/146	297/1244	1.29 (0.88-1.89)	1.36 (0.90-2.06)
0	104	947	1.00 ...	1.00 ...
1-15	26	177	1.34 (0.85-2.12)	142 (0.85-2.35)
16-30	7	68	0.94 (0.42-2.09)	0.89 (0.37-2.15)
>30	9	52	1.58 (0.76-3.29)	1.90 (0.84-4.31)
			Trend P=.23	Trend P=.16

*Adjusted for age; race; study area; education; fruits, vegetables, and supplemental vitamin index; dietary cholesterol; family history of lung cancer; and employment in high-risk occupations. OR indicates odds ratio; CI, confidence interval.
†P<.05.
‡P<.01.
§P<.001.
¶Social exposure is defined as exposure of 2 or more hours per week from sources other than occupational and household.

considered jointly, statistically significant increasing risks with increasing duration of exposure are observed for all lung cancers combined (trend P=.0001), adenocarcinomas (trend P=.001), and for cell types other than adenocarcinoma (trend P=.05). At the highest level of exposure, a 75% increased risk is observed. Similar and statistically significant trends in risk are observed with analyses restricted to self-respondents for all lung cancers combined and adenocarcinomas. For other histological types, a significant trend is no longer observed. Similar positive trends were observed regardless of pathology review status and within all levels of the fruits, vegetables, and supplemental vitamin use index; dietary cholesterol intake; age; and race; although the risk estimates and trends were somewhat stronger among white study subjects and women younger than 70 years.

To determine whether risk associated with adult ETS exposure differs according to childhood exposure status, the data were stratified by childhood exposure (Table 8). Elevated risks associated with adult ETS exposures were observed in women with (trend P=.01) and without (trend P=.0005) childhood exposures, but the elevations in risk for women exposed during childhood were about twice as high as those without childhood exposures. At the highest level of exposure (48 adult smoke-years or more), an adjusted OR of 3.25 (95% CI, 2.42 to 7.46) was observed among women reporting childhood exposure compared with 1.77 (95% CI, 0.98 to 3.19) for those reporting no childhood exposure. The estimates based on self-responses only indicate a similar pattern of risk. Although the differences are approximately twofold, the CIs for the ORs at each level of exposure overlap.

COMMENT

In this report, the RR of lung cancer associated with ETS exposure was assessed for all lung cancers, adenocarcinoma of the lung alone, and other histopathologic cell types combined. Throughout, the increased risks associated with adult ETS exposures were quite consistent for adenocarcinoma and other cell types and, as a result, for all lung cancers combined. Compared with adenocarcinoma cases, the number of other cell types was quite small; therefore, the failure to observe statistically significant trends in this group is more likely a result of lower statistical power than biological differences in response in the two histopathologic subgroups. For example, the power to detect an OR of 1.3 associated with ever use of tobacco by a spouse was approximately 73% for all lung cancer cases, 65% for adenocarcinoma, and 31% for other cell types combined. In the 3-year report of the study, increased risk of lung cancer from adult ETS exposure was stronger for adenocarcinoma of the lung than for all cell types combined.[2] That finding is no longer apparent with the additional cases of each cell type. Although the estimates of RR for pulmonary adenocarcinoma are not different from those for other cell types, adenocarcinoma of the lung is by far the predominant cell type diagnosed in women with lung cancer who are lifetime nonsmokers, and so the effects of ETS exposure may be particularly relevant for this histopathologic cell type. More than 75% of the cases in this study were diagnosed with primary pulmonary adenocarcinoma, twice the proportion of adenocarcinoma of the lung diagnosed in all US women without regard to smoking history: 37% among female lung cancer cases in the SEER program.[43] In other studies of ETS in female nonsmokers in which histopathology was reported, adenocarcinoma comprised 60% or more of all cases in six of nine studies.[2,9,14,26,32,33] In the other three studies, the proportion of adenocarcinoma cases ranged from 43% to 54%.[5,7,11] Differences in the physical and chemical properties of sidestream smoke compared with mainstream smoke, including the distribution of the vapor and particulate phases and the concentration of known or suspected carcinogens,[44] combined with differences in inhalation, nasal vs oral, may yield a higher proportion of peripheral adenocarcinomas.[45]

Misclassification of disease status was minimized in this study by the eligibility criteria (microscopic diagnosis required) and an independent review of diagnostic material that was completed for 85% of the cases. The small proportion of cases found ineligible by independent review may result from the population-based tumor registry affiliation of four of the five study centers. The consistency of the findings with and without nonreviewed cases supports the contention that the study results were not measurably altered by inclusion of ineligible cases.

Misclassification of ever smokers as lifetime never smokers is more problematic. The objective of this study was to evaluate the risk of lung cancer in women who had never smoked. At present there is no known biomarker of lifetime tobacco use. Cotinine, the major metabolite of nicotine, is the most widely accepted biomarker of current (1 to 2 days) tobacco exposure and is useful for distinguishing current active smokers from current nonsmokers.[1,44] The proportion of reported nonsmokers in the present study with a cotinine/creatinine concentration above 100 ng/mg was 1.9%, the same proportion with a concentration above 100 ng/mg observed in a 10-country, multicenter study of self-reported ETS exposure.[46]

Table 7.—Association Between Risk of Lung Cancer and Adulthood Smoke-Years of Exposure Among Nonsmoking Women*

Adult Smoke-Years of Exposure	Cases	Controls	Crude OR (95% CI)	Adjusted OR (95% CI)
All Lung Carcinomas (All Respondents)				
0	48	118	1.00 ...	1.00 ...
1-11	74	239	0.76 (0.50-1.16)	0.82 (0.52-1.29)
12-28	138	307	1.11 (0.75-1.63)	1.12 (0.73-1.70)
29-47	153	304	1.24 (0.84-1.82)	1.35 (0.89-2.04)
≥48	163	265	1.51 (1.03-2.23)†	1.74 (1.14-2.65)†
			Trend P=.0001	Trend P=.0001
Adenocarcinoma (All Respondents)				
0	36	118	1.00 ...	1.00 ...
1-11	54	239	0.74 (0.46-1.19)	0.74 (0.44-1.23)
12-28	110	307	1.17 (0.76-1.81)	1.15 (0.73-1.83)
29-47	112	304	1.21 (0.78-1.86)	1.29 (0.81-2.04)
≥48	130	265	1.61 (1.05-2.47)†	1.77 (1.12-2.80)†
			Trend P=.0002	Trend P=.0001
Other Histological Types (All Respondents)				
0	12	118	1.00 ...	1.00 ...
1-11	20	239	0.82 (0.39-1.74)	1.17 (0.52-2.62)
12-28	28	307	0.90 (0.44-1.82)	1.00 (0.46-2.18)
29-47	41	304	1.33 (0.67-2.61)	1.58 (0.76-3.31)
≥48	33	265	1.23 (0.61-2.46)	1.76 (0.83-3.75)
			Trend P=.12	Trend P=.05
All Lung Carcinomas (Self-respondents Only)				
0	30	118	1.00 ...	1.00 ...
1-11	53	238	0.88 (0.51-1.54)	0.79 (0.44-1.42)
12-28	103	306	1.32 (0.84-2.10)	1.20 (0.74-1.94)
29-47	110	304	1.42 (0.90-2.25)	1.44 (0.89-2.31)
≥48	105	265	1.56 (0.98-2.47)	1.67 (1.03-2.70)†
			Trend P=.002	Trend P=.0006
Adenocarcinoma (Self-respondents Only)				
0	23	118	1.00 ...	1.00 ...
1-11	41	238	0.88 (0.53-1.44)	0.81 (0.48-1.37)
12-28	88	306	1.48 (0.89-2.45)	1.31 (0.77-2.22)
29-47	82	304	1.38 (0.83-2.30)	1.39 (0.82-2.36)
≥48	91	265	1.76 (1.06-2.92)†	1.85 (1.09-3.15)†
			Trend P=.001	Trend P=.0005
Other Histological Types (Self-respondents Only)				
0	7	118	1.00 ...	1.00 ...
1-11	12	238	0.85 (0.33-2.22)	0.91 (0.34-2.45)
12-28	15	306	0.83 (0.33-2.08)	0.82 (0.31-2.16)
29-47	28	304	1.55 (0.66-3.65)	1.64 (0.67-4.03)
≥48	14	265	0.89 (0.35-2.26)	1.12 (0.42-2.96)
			Trend P=.49	Trend P=.32

*Adjusted for age; race; study area; education; fruits, vegetables, and supplemental vitamin index; dietary cholesteroi; family history of lung cancer; and employment in high-risk occupations. OR indicates odds ratio; CI, confidence interval.
†P<.05.

A higher proportion of controls than cases was excluded from the study as a result of elevated concentrations of urinary cotinine/creatinine, 2.3% vs 0.6%. Cases were identified at hospitals, and screening of medical records and physicians about the patient's current and past use of tobacco preceded the screening by telephone and at the interview for all study subjects. This procedure may have eliminated some current smokers from the case series who would have been inclined to self-report as nonsmokers in an interview format. Alternatively, some cases who would misreport smoking status may be less likely, because of health status, to be actively smoking and less likely to be revealed than healthy, free-living controls. Other data suggest that lung cancer cases who are ever smokers may be less inclined to misreport smoking status than others in the general population: the proportion of ever smokers misclassified as nonsmokers by discordant reports was 1% among female lung cancer cases from five case-control studies and 5.7% among subjects from general population studies.[1] Neither cases nor controls were informed before the interview that a urine sample would be requested to eliminate the opportunity for avoidance of personal tobacco use or substitution of specimens.

Table 8.—Association Between Risk of Lung Cancer and Adulthood Smoke-Years Among Nonsmoking Women With and Without Childhood Exposures*

Smoke-Years of Exposure During Adulthood	No Childhood Exposure				Childhood Exposure			
	Cases	Controls	Crude OR (95% CI)	Adjusted OR (95% CI)	Cases	Controls	Crude OR (95% CI)	Adjusted OR (95% CI)
All Lung Carcinomas vs Controls (All Respondents)								
0	33	71	1.00 ...	1.00 ...	8	44	1.00 ...	1.00 ...
1-11	33	91	0.78 (0.44-1.39)	0.76 (0.40-1.43)	38	137	1.53 (0.66-3.52)	1.63 (0.69-3.86)
12-28	41	97	0.91 (0.52-1.58)	0.80 (0.43-1.46)	88	202	2.40 (1.08-5.30)	2.43 (1.07-5.51)†
29-47	54	97	1.20 (0.71-2.04)	1.16 (0.65-2.06)	85	204	2.29 (1.04-5.07)	2.64 (1.16-6.01)†
≥48	54	80	1.45 (0.85-2.49)	1.77 (0.98-3.19)	94	182	2.84 (1.29-6.28)	3.25 (1.42-7.46)‡
			Trend P=.04	Trend P=.01			Trend P=.0013	Trend P=.0005
All Lung Carcinomas vs Controls (Self-respondents Only)								
0	23	71	1.00 ...	1.00 ...	5	44	1.00 ...	1.00 ...
1-11	23	90	0.79 (0.41-1.52)	0.68 (0.34-1.38)	29	137	1.86 (0.68-5.10)	1.85 (0.66-5.21)
12-28	28	97	0.89 (0.47-1.67)	0.64 (0.32-1.28)	69	201	3.02 (1.15-7.93)†	2.99 (1.11-8.05)†
29-47	36	97	1.15 (0.63-2.10)	1.04 (0.54-1.98)	67	204	2.89 (1.10-7.59)†	3.33 (1.23-9.00)†
≥48	31	80	1.20 (0.64-2.24)	1.34 (0.69-2.60)	70	182	3.39 (1.29-8.89)†	3.83 (1.41-10.42)‡
			Trend P=.26	Trend P=.17			Trend P=.004	Trend P=.001

*Adjusted for age; race; education; study area; fruits, vegetables, and supplemental vitamin index; dietary cholesterol; family history of lung cancer; and employment in high-risk occupation. OR indicates odds ratio; CI, confidence interval.
†P<.05.
‡P<.01.

Refusal to provide a sample was similar among living cases (19%) and controls (17%); however, because of illness and death, a higher proportion of the total subjects in the case series had no cotinine measurement. Of study subjects for whom no sample was available, 63% reported ever having lived with a spouse who smoked; for study subjects with cotinine determinations, 63% of eligible women and 68% of excluded women reported ever having spousal ETS exposure.

Analyses using a lower cut point (55 mg/ng) for exclusion based on urinary cotinine concentrations provided slightly higher estimates of risk associated with ETS exposure, but the differences have little or no effect on study conclusions.

Compared with recent large US studies, the proportion of proxy respondents for lung cancer cases in this study was small: 36.9% compared with 65% in the study reported by Brownson et al[33] and 67% in the study by Stockwell et al.[34] Nevertheless, it is important to evaluate whether the findings differ when proxy respondents are excluded from the analyses. The only appreciable difference was noted for childhood exposures. Of those interviews with proxy respondents, 31% were conducted with the study subject's spouse and 48% with an adult offspring of the study subject. These individuals had lived with the study subject and shared life experiences during the study subject's adult life, but not during the study subject's childhood years. The opportunity for misclassification of exposures is greater, therefore, for childhood exposures. The lower reliability for childhood exposures compared with estimates of exposure from a spouse has been noted previously.[46,47] The consistency of findings for adult-life exposures in the total series and among self-respondents only suggests that systematic misclassification by proxy respondents for adult-life ETS exposures was minimal.

The inconsistency in the literature with regard to the association of lung cancer with ETS exposure during childhood[3,7,12,23,26,29,32,33] may stem from the limited power of many of these studies, as well as difficulties in recall of distant events and/or incomplete knowledge by proxy respondents. The effect of each of these factors is likely to vary among different cultures, as well as by the proportion of proxy respondents in any given study. Failure to find an independent effect of childhood exposure in case-control studies might result also from the latency period of lung cancer and the age distribution of female nonsmokers with lung cancer. Lung cancer arising as a result of childhood ETS exposure would be expected to occur relatively early in life. Even with a latent period of 30 or 40 years, these cases would be younger than 60 years at the time of diagnosis, and such cases comprise a small part of the total case series. No differences were observed in this study, however, when risk associated with smoke-years of exposure during childhood was examined for subjects in the case and control groups who were younger than 60 years compared with those 60 years of age and older. Although no independent effect of childhood exposure was observed, such exposure appears to modify the effect of subsequent ETS exposure during adult life. Twofold increases in risk are observed at all levels of adult exposure for subjects who had any childhood household exposure compared with those who did not.

Individual nutrients and micronutrients associated with lung cancer were included in preliminary analyses. The final model includes an index that captures the intake of both dietary and supplemental antioxidants and a variable for dietary intake of cholesterol adjusted for calories. In this study, high intake of fruits and vegetables and supplemental vitamins is associated with decreased risk of lung cancer, and dietary cholesterol is associated with increased risk. Although it has been suggested that low intake of carotenoids or fruits and vegetables and high intake of dietary fat are potential confounders of the association between ETS and lung cancer,[48] this was not observed in our study or in the recent report by Kalandidi et al.[15] In addition, similar trends of increased risk of lung cancer associated with increasing smoke-years of exposure are apparent at all levels of both dietary cholesterol intake and the index of fruits, vegetables, and supplemental vitamin use. Household radon was measured by 48-hour passive diffusion canisters in a sample of study subjects' homes, and these screening levels in all five geographic areas were uniformly low and not associated with case-control status. These observations indicate that the strong association in this study between adult ETS exposure and lung cancer risk cannot be attributed to any likely confounder.

A positive dose response between ETS exposure during adult life and lung cancer risk was found when individual sources of exposure, such as household, occupational, and social settings, were examined separately, and this pattern of risk was clearest when these exposure sources were considered jointly. The point estimates are somewhat higher for exposures in occupational and social settings than within households, but these differences are not statistically significant. The higher estimates in the former settings may reflect chance, some recall bias, or the potential for a larger number of smokers and smoke exposures in these settings. Workplace ETS exposure has received less attention than domestic ETS exposure in studies of lung cancer to date; however, monitoring of ETS or its constituents in workplace settings has demonstrated detectable markers of ETS by personal air monitoring and biomarkers with average concentrations similar to residential levels but with higher maximum values.[1] In a study of workplace ETS, the correlation between number of smokers encountered during a workshift and personal sampler nicotine concentration (micrograms per cubic meter) was 0.62 (P<.05) and with postshift urinary cotinine was 0.63 (P<.05).[49] Brunnemann et al[50] sampled indoor air in bars, restaurants, and trains and found carcinogenic tobacco-specific N-nitrosamines at concentrations up to 23 pg/L of N'-nitrosonornicotine and 29 pg/L of 4-(methylnitrosamino)-1-(3 pyridyl)-1-butanone. These settings serve as workplaces for employees and social settings for patrons. The significant elevated risk of lung cancer in this study associated with exposures outside the home suggests the importance of these settings, in addition to spousal ETS exposure, in the United States.

The findings of this study support the conclusion that long-term exposure to ETS increases risk of lung cancer in women who have never personally used tobacco. This increased risk is more marked for women who have also been exposed to ETS during childhood.

This research was supported by grant CA40095 from the National Cancer Institute, Bethesda, Md, with additional support from the Louisiana Cancer and Lung Trust Fund Board and the Louisiana State University Stanley S. Scott Cancer Center, New Orleans.

The authors are grateful for the cooperation of all of the participating hospitals in the five study areas and the many physicians who helped make this study possible. The authors also thank Gladys Block, PhD, for her thoughtful comments and suggestions, particularly related to dietary exposures; S. Donald Greenberg, MD, for the microscopic review of diagnostic material; Christopher Powers, MS, Gail Smith, Mahboob Sobhan, PhD, and William Johnson, MS, for programming and analytic support; Laurel Cederquist, MS, Annie Fung, Judy Goldstein, Helen Gregory, and Anne Morse for field supervision; the American Health Foundation for conducting the urinary cotinine analyses; and the dedicated medical record abstractors and interviewers in each study center.

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