

Lung Cancer in Nonsmoking Women: A Multicenter Case-Control Study¹

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Abstract

The association between exposure to environmental tobacco smoke and lung cancer in female lifetime nonsmokers was evaluated using data collected during the first 3 years of an ongoing case-control study. This large, multicenter, population-based study was designed to minimize some of the methodological problems which have been of concern in previous studies of environmental tobacco smoke and lung cancer. Both a cancer control group and a population control group were selected in order to evaluate recall bias. A uniform histopathological review of diagnostic material was conducted for case confirmation and detailed classification. Biochemical determination of current exposure to tobacco and screening of multiple sources of information to determine lifetime nonuse were utilized to minimize misclassification of smokers as nonsmokers.

A 30% increased risk of lung cancer was associated with exposure to environmental tobacco smoke from a spouse, and a 50% increase was observed for adenocarcinoma of the lung. A statistically significant positive trend in risk was observed as pack-years of exposure from a spouse increased, reaching a relative risk of 1.7 for pulmonary adenocarcinoma with exposures of 80 or more pack-years. The predominant cell type of the reviewed, eligible lung cancer cases was adenocarcinoma (78%). Results were very similar when cases were compared to each control group and when separate analyses were

conducted for surrogate and personal respondents. Other adult-life exposures in household, occupational, and social settings were each associated with a 40-60% increased risk of adenocarcinoma of the lung. No association was found between risk of any type of lung cancer and childhood exposures from a father, mother, or other household members.

Introduction

Approximately one decade has passed since the initial reports of increased risk of lung cancer in nonsmoking women married to smokers (1, 2). The ensuing studies have provided a body of data which suggests a small but significant elevation in risk of lung cancer associated with exposure to ETS³ (3-22). In reported prospective studies exposure has been assessed by the spouse's smoking history, primarily that of husbands. In case-control studies, the primary ETS exposure assessed has also been that from a spouse, although exposures from parents, other household exposures, and the workplace have been examined in some studies.

In general, these studies have included fewer than 100 nonsmoking lung cancer cases whose self-reported smoking status has not been validated by biochemical determination or other means. Reviews of available studies of ETS and lung cancer in nonsmokers by the National Research Council (23), the International Agency for Cancer Research (24), and others (25, 26) have concluded that although misclassification is unlikely to account for all of the observed increased risk, some misclassification of current or former smokers as nonsmokers is likely (0.5-5.0%). Because smokers tend to marry smokers, misreporting may introduce some bias in the estimation of the magnitude of the observed effect.

This study was undertaken in 1985 in an effort to address a number of unresolved issues related to ETS:

(a) *Misclassification of Smoking Status.* Multiple sources of information are utilized to ascertain nonsmoking status (medical record, physician, and then the study subject or surrogate). Study respondents are questioned twice (at contact to set up the interview and at the beginning of the interview). Self-reported current nonsmoking status is corroborated by measurement of urinary cotinine.

(b) *Histopathological Specificity.* Microscopic diagnostic slides are reviewed by one pulmonary pathologist both to confirm eligibility of cases as primary lung carcinomas and to provide a detailed review (subtype, differ-

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³ The abbreviations used are: ETS, environmental tobacco smoke; SEER, Surveillance, Epidemiology, and End Result; OR, odds ratio; CI, confidence interval.

entiation) and classification of the histopathological cell type.

(c) *Recall Bias.* Two control groups, one with colon cancer and one from the general population, are selected for case-control comparisons. Differential recall between cases and colon cancer controls should be minimized since both groups are similarly motivated to recall earlier exposures.

(d) *Source of ETS Exposure.* Information on childhood exposures from a father, mother, and other household members and adult exposures from husband(s), other household members, and occupational and social settings is obtained by questionnaire. The risk associated with exposure to ETS from different sources and during different time periods can be evaluated.

(e) *Confounders and Other Risk Factors.* Because the magnitude of the main ETS effect is expected to be small, it is important to take into account potential confounding factors and effect modifying factors in a study with a sufficiently large number of cases and controls. It is anticipated that upon completion of this study about 600 cases and twice that number of controls will have participated.

This report represents findings from the ongoing study and includes the largest number of lifetime nonsmokers with lung cancers reported to date. This report was felt to be justified given the public health importance of the issue under investigation.

Methods

The study is a population-based case-control study of lung cancer in women who have never used any tobacco product. This preliminary report includes cases diagnosed during the first three years (December 1, 1985 through December 31, 1988) of a 5-year study. At the time of diagnosis cases were residents of one of five major metropolitan areas throughout the United States, including Atlanta (Clayton, Cobb, DeKalb, Fulton, and Gwinnett counties), Houston (Galveston and Harris counties), Los Angeles (Los Angeles County), New Orleans (Jefferson, Orleans, and St. Bernard parishes), and the San Francisco Bay Area (Alameda, Contra Costa, Marin, San Francisco, San Mateo, and Santa Clara counties), representing a population of approximately 18.5 million people or 8% of the U. S. population.

Case and Control Selection

Rapid case ascertainment procedures, which included review of pathology reports from study hospitals, were utilized to identify potentially eligible lung cancer cases. Eligible cases included English-, Spanish-, or Chinese-speaking females, aged 20-79, who had a histopathologically confirmed diagnosis of primary carcinoma of the lung (International Classification of Disease, 9th Revision, code 162) made prior to death, had no history of previous cancer, and who were lifetime nonusers of tobacco. Lifetime nonusers of tobacco are defined for this study as persons who had smoked fewer than 100 cigarettes and had not used any other form of tobacco for more than 6 months.

Two control groups were selected. The first control group, referred to as the population control group, was selected by random digit dialing and supplemented by random sampling from the files of the Health Care Fi-

nancing Administration for women aged 65 and older. Controls were frequency matched to cases on age (<50, 50-59, 60-69, 70+ years) in a 2:1 control:case ratio. They met the same eligibility criteria as cases for age, residence, language, and tobacco use.

Females, aged 20-79, with a diagnosis of primary carcinoma of the colon (International Classification of Disease, 9th Revision, code 153) who met the language, previous cancer, lifetime nonsmoking, and residential eligibility criteria of the cases, were identified and frequency matched to lung cancer cases by 10-year age groups and race. This second control group was selected because there is no established increased risk of colon cancer associated with either active or passive smoking, and it provided an opportunity to examine the issue of recall bias associated with a recent diagnosis of cancer.

A multistep procedure was used to determine lifetime smoking status. After identification of a potentially eligible lung cancer case or colon cancer control, the hospital chart was reviewed to obtain demographic data and available information on tobacco use. Patients identified as current or former smokers in the medical record were considered ineligible. In study areas where individual physician notification was required/preferred, the tobacco use history was requested from the physician for potentially eligible cases and colon controls identified as nonusers of tobacco or with unknown smoking status according to the hospital record. Women who were identified as current or former smokers by their physicians were considered ineligible. All remaining cases and colon cancer controls believed to be nonsmokers or with unknown smoking status were contacted by telephone to elicit information on tobacco use. Women who reported ever smoking 100 or more cigarettes or using any other form of tobacco for more than 6 months were considered ineligible. The identical telephone screening procedure was used for the population control group. At the time of the interview, the tobacco use screening questions were repeated to confirm each study subject's reported nonuse of tobacco.

The questionnaire was translated from English into Spanish and Chinese, and interviewers fluent in those languages conducted the non-English as well as English interviews. Interviews were completed for 431 of 514 incident cases (84%), 358 of 489 colon cancer controls (73%), and 794 of 1105 population controls (72%). Sixty-one (3.8%) of the interviews were conducted in Spanish ($n = 14$) or Chinese ($n = 47$): 22 cases (5%); 23 colon cancer controls (6%); and 16 population controls (1.5%). A next-of-kin interview was solicited for lung cancer cases and colon cancer controls who were too ill or deceased. All population controls were self-respondents because of the sampling method used to identify these controls. A total of 143 lung cancer case interviews and 35 of 352 colon cancer control interviews were conducted with next-of-kin respondents, representing 34% and 10% of the eligible respondents.

An extensive structured questionnaire obtained information concerning household, occupational, and other exposures to environmental tobacco smoke during the study subject's lifetime. Data were also collected on lifetime occupational history, usual adult diet, family and personal medical histories, and other exposures of interest, which are not included in this report.

Table 1 Urinary cotinine/creatinine (ng/mg) by case-control status

	Lung cancer cases	Colon cancer controls	Population controls
Status			
Completed	239	260	684
Eligible (<100 ng/mg)	237	253	670
Ineligible (≥ 100 ng/mg)	2	7	14
Not performed			
Self-respondents	58	66	110
Next-of-kin respondents	134	32	
Results			
Eligible (<100 ng/mg)			
Mean (SD)	6.95 (12.11)	5.82 (11.68)	9.68 (12.88)
Median	2.0	0	5.4
Range	0-71.4	0-88.4	0-95.01
Ineligible (≥ 100 ng/mg)			
Range	131-219	145-5,163	103-14,014

Eligibility Review Procedures

Biochemical Determination of Current Tobacco Use. Cotinine, a major metabolite of nicotine, is an indicator of recent exposure to tobacco (27). Urinary cotinine was used to corroborate self-reported current nonsmoking status of study subjects. A urine sample was collected from all consenting study subjects at the time of interview. The specimens were stored at -20°C until shipment to the American Health Foundation for analysis.

Cotinine was quantitated by radioimmunoassay using the method of Haley et al. (28) with a modification of the antibody of Langone et al. (29). Cotinine levels were adjusted for urine flow based on creatinine values by determining the cotinine/creatinine ratio. Creatinine was determined by spectrophotometry using the Kodak Ektachem 400 Clinical Chemistry Analyzer.

At this time biochemical analysis is complete for 239 of 431 cases (55.5%), 260 of 358 colon cancer controls (72.6%), and 684 of 794 population controls (86.1%) (Table 1). Two of 239 case samples (0.8%), 7 of 260 colon cancer control samples (2.6%), and 14 of 684 population control samples (2.0%) had cotinine/creatinine levels of 100 ng/mg or greater. There is no established cotinine/creatinine level which clearly discriminates smokers from true nonsmokers heavily exposed to ETS. Under relatively high levels of exposure to ETS in aircraft and in exposure chambers, urinary excretion has reached a level of 55 ng/mg creatinine (30, 31). In this study, women whose cotinine/creatinine level exceeded 100 ng/mg were excluded from the study to eliminate persons likely to be active smokers, while allowing for the possibility of very high ETS exposures reflected in urinary levels of 56-99 ng/mg creatinine. Had the lower value of 55 ng/mg been selected as a cutpoint to avoid possible misclassification of active smokers as nonsmokers, 4 additional cases (1.6%), 2 colon cancer controls (0.8%), and 13 population controls (1.9%) would have been excluded from the analyses, with negligible effect on the results.

Histopathological Review. Representative diagnostic microscopic tissue slides for each case were requested from the hospital. These slides were reviewed by one pathologist specializing in pulmonary pathology. A total of 368 of 429 (86%) potential cases have undergone review. As shown in Table 2, 359 (98%) of the reviewed cases were confirmed as primary bronchogenic carcinoma. The his-

Table 2 Pathology review

Reviewed, found to be eligible	359 (85%)
Adenocarcinoma	281
Large cell carcinoma	43
Squamous cell carcinoma	20
Small cell carcinoma	12
Others and not otherwise specified	3
Not reviewed/insufficient material	50 (12%)
Histology by hospital pathologist	
Adenocarcinoma	30
Large cell carcinoma	5
Squamous cell carcinoma	7
Small cell carcinoma	2
Others and not otherwise specified	6
Review pending	11 (3%)
Total cases	420
Reviewed, found to be ineligible	9

topathological primary cell type of the eligible cases is as follows: adenocarcinoma, 78%; large cell carcinoma, 12%; squamous cell carcinoma, 6%; small cell carcinoma, 3%; others, 1%. The histopathological cell type distributions were similar in the five study centers.

The overall concordance between the review pathology diagnosis and the original hospital pathology diagnosis was 81% (Table 3). The concordance varied greatly by histopathological cell type. Ninety-seven % (237 of 244) of the cases originally classified as adenocarcinomas were confirmed as this histopathological type upon review. Similarly, 10 of 11 (91%) of small cell carcinomas were so classified upon review. Concordance rates of 56% and 67% were seen for large cell and squamous cell carcinomas, respectively. A relatively large proportion of cases originally classified as large cell or squamous cell carcinomas were classified as adenocarcinomas by the review pathologist: 18 of 46 (39%) and 6 of 24 (25%), respectively. Based on hospital pathology reports, 34 subjects were categorized as "other primary lung carcinomas" which primarily included diagnoses of poorly differentiated carcinoma, bronchogenic carcinoma not otherwise specified, or malignant cells not otherwise specified. Upon review, 94% of these cases were classified into more specific histopathological cell types.

The nine cases (2%) found not to have primary bronchogenic carcinoma on review were excluded from all analyses. Three of these nine cases were determined to be carcinoid tumors, two were lymphomas, three were carcinomas metastatic to the lungs from other primary sites, and one was a benign neoplasm. The 61 cases that have not undergone histopathological review are included in analyses of all lung cancers combined ($n = 420$) but are not included in analyses stratified by histopathological type.

Statistical Analyses

Exposure to ETS was examined by source. Sources include both adult and childhood exposures as follows: spouse, other household members; occupational ETS exposures; and social or leisure time (nonhousehold, nonoccupational) ETS during adult life; and father, mother, and other household members who lived in the

Table 3 Distribution of lung cancer histopathological cell types by hospital diagnosis and review diagnosis

Review diagnosis	Hospital diagnosis					Total
	Adenocarcinoma	Large cell carcinoma	Squamous cell carcinoma	Small cell carcinoma	Other lung carcinoma	
Adenocarcinoma	237	18	6	1	19	281
Large cell carcinoma	6	26	1	0	10	43
Squamous cell carcinoma	0	2	16	0	2	20
Small cell carcinoma	0	0	1	10	1	12
Other primary lung carcinomas	1	0	0	0	2	3
Total	244	46	24	11	34	359

home 6 months or more during childhood. Childhood was defined as the first 18 years of life. Exposures from parents after that time were classified as other household members during adult life. Dichotomous ETS exposures were first examined (ever or never) by type of tobacco: cigarettes; pipe; cigar; or any of these types of tobacco. Dose was estimated, as appropriate, by intensity (e.g., number of cigarettes/day), duration (e.g., number of years exposed), or a combination (e.g., pack-years). Pack-years of cigarette exposure from the 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. Pack-years of exposure were summed for all smoking spouses of each study subject.

One of the objectives of this study was to evaluate the association of ETS with specific histopathological cell types of lung cancer. The skewed distribution of histopathological types precluded any meaningful analysis by specific cell type other than adenocarcinoma and all other cell types combined. The results are presented for all lung cancers combined ($n = 420$) and adenocarcinoma as confirmed by histopathological review ($n = 281$).

Cases were compared to each control group with regard to the distribution of relevant covariates such as age, education, income, and race/ethnicity. The association of ETS exposure with lung cancer risk was investigated first in contingency tables stratified by design or sampling variables (age, race, study center) and relevant covariates. Summary adjusted odds ratios and test statistics were calculated by the method of Mantel and Haenszel (32). Unconditional logistic regression analyses were then used to estimate the associations by summary adjusted odds ratios, confidence limits, and test statistics (33, 34).

Results

Demographic characteristics of cases and controls are presented in Table 4. Cases and controls were similar with respect to matching variables and most demographic variables. The largest number of cases ($n = 160$, 38%) were residents of Los Angeles, followed by cases from the San Francisco Bay Area ($n = 149$, 35%), and then the three smaller study centers in the southern United States: Atlanta ($n = 46$, 11%); Houston ($n = 39$, 9%); and New Orleans ($n = 26$, 6%).

The age distribution of cases and controls is uniform, with 73 to 74% of each series between the ages of 60 through 79. The proportion of older women in this group of female nonsmokers with lung cancer is higher than

that among all female lung cancer cases in the SEER Program 1974-1986, in which only 48% of the cases were aged 65 or older (35).

Cases tended to have a somewhat lower household income and less education than the population controls. Approximately 35% of cases and controls spent their childhood in cities with populations of 50,000 or more, and the majority of cases and controls (70%, 68%, 77% for cases, colon cancer controls, and population controls, respectively) resided in cities during most of their adult life.

The estimated risks of lung cancer in nonsmoking women associated with ever having lived with a spouse who smoked are presented in Table 5. The adjusted ORs and the 95% CI are very similar for all spouse-related exposures regardless of control group. For all histopathological types of lung cancer combined, a 30% increase in risk is observed (OR = 1.28 and 1.29 with colon cancer and population controls). For each of the three types of tobacco smoked, the ORs ranged from 1.14 to 1.26. When the case series is restricted to the 281 pulmonary adenocarcinomas confirmed by histopathological review, the association is more pronounced. Approximately 50% elevations in risk of adenocarcinomas of the lung ($P < 0.05$) are associated with any use of tobacco by spouse(s), and cigarette smoking accounts for most of the tobacco use. The estimated relative risk of pulmonary adenocarcinoma associated with cigarette smoking by spouses was 1.36 (1.02-1.84) with the population controls as comparison and 1.31 (0.94-1.84) with the colon cancer controls as comparison. No association between spouses' tobacco use and lung cancers other than adenocarcinoma (squamous cell, small cell, large cell, and other; $n = 78$) was observed.

Separate analyses were conducted for subjects who personally responded and for whom information was obtained from surrogate respondents. The odds ratios for involuntary exposure to ETS were very similar for both groups of respondents; therefore, the results are not presented in the tables separately by type of respondent. One such example is the estimated relative risk of pulmonary adenocarcinomas associated with cigarette smoking by the spouse: OR = 1.38 and 1.30 for surrogate and self-respondents, respectively, comparing cases to colon cancer controls.

Effects by study center were also examined. The odds ratios by center ranged from a low of 1.17 to a high of 2.64 for risk of pulmonary adenocarcinoma associated with spouses' cigarette smoking. Because of the limited sample sizes, none of the individual study center esti-

Table 4 Distribution of lung cancer cases and controls according to selected demographic characteristics

	Lung cancer cases (n = 240)		Colon cancer controls (n = 351)		Population controls (n = 780)	
	No.	(%)	No.	(%)	No.	(%)
Study center						
Atlanta	46	(11.0)	44	(12.5)	76	(9.7)
Houston	39	(9.3)	35	(10.0)	24	(3.1)
Los Angeles	160	(38.1)	125	(35.6)	358	(45.9)
New Orleans	26	(6.2)	18	(5.1)	44	(5.6)
San Francisco Bay Area	149	(35.5)	129	(36.7)	278	(35.6)
Respondent						
Study subject	277	(66.0)	316	(90.1)	780	(100.0)
Next of kin	143	(34.0)	35	(9.9)		
Age (years)						
20-29	5	(1.2)	1	(0.3)	9	(1.2)
30-39	11	(2.6)	13	(3.7)	42	(5.4)
40-49	23	(5.5)	22	(6.3)	30	(3.9)
50-59	73	(17.3)	55	(15.6)	121	(15.5)
60-69	147	(35.0)	105	(29.8)	221	(28.3)
70-79	161	(38.3)	155	(44.0)	357	(45.8)
Race/ethnic group						
White	266	(63.3)	240	(68.5)	503	(64.5)
Black	44	(10.5)	59	(16.8)	107	(13.7)
Hispanic	32	(7.6)	14	(4.0)	42	(5.4)
Asian	67	(16.0)	35	(10.0)	113	(14.5)
Other	11	(2.6)	2	(0.6)	13	(1.7)
Unknown/refused to answer	0	(0.0)	1	(0.2)	2	(0.4)
Annual income						
<\$8,000	72	(17.1)	60	(17.1)	98	(12.6)
\$8,000-12,999	63	(15.0)	52	(14.8)	115	(14.7)
\$13,000-19,999	48	(11.4)	48	(13.7)	110	(14.1)
\$20,000-34,999	73	(17.4)	61	(17.4)	153	(19.6)
\$35,000-49,999	37	(8.8)	49	(14.0)	82	(10.5)
≥\$50,000	59	(14.1)	35	(10.0)	128	(16.4)
Unknown/refused to answer	68	(16.2)	46	(13.1)	94	(12.0)
Education						
Less than high school	135	(32.1)	84	(23.9)	165	(21.2)
High school	140	(33.3)	134	(38.2)	246	(31.5)
Some college	71	(16.9)	74	(21.1)	181	(23.2)
College	33	(7.9)	28	(8.0)	107	(13.7)
Graduate	25	(6.0)	22	(6.3)	69	(8.9)
Unknown	16	(3.8)	9	(2.6)	12	(1.5)
Usual childhood residence						
Farm	93	(22.1)	78	(22.2)	131	(16.8)
Rural area	49	(11.7)	36	(10.3)	61	(7.8)
<20,000 population	92	(21.9)	81	(23.1)	196	(25.1)
20,000-49,999 population	37	(8.8)	46	(13.1)	98	(12.6)
≥50,000 population	146	(34.8)	109	(31.1)	291	(37.3)
Unknown	3	(0.7)	1	(0.3)	3	(0.4)
Usual adult residence						
Farm	23	(5.5)	15	(4.3)	10	(1.3)
Rural area	10	(2.4)	6	(1.7)	13	(1.7)
<20,000 population	39	(9.3)	28	(8.0)	45	(5.8)
20,000-49,999 population	53	(12.6)	61	(17.4)	108	(13.9)
≥50,000 population	293	(69.8)	240	(68.4)	601	(77.0)
Unknown	2	(0.5)	1	(0.3)	3	(0.4)

mates were statistically significant, and they did not significantly differ from one another.

Estimates of relative risk associated with the number of cigarettes smoked by a spouse were significantly elevated only in the highest exposure category, 40 or more

cigarettes/day: 2.06 (1.19-3.54) and 1.69 (1.28-2.61) for adenocarcinoma of the lung comparing cases to colon cancer and population controls, respectively. Odds ratios were similar, although slightly lower, for all types of lung cancer combined: 1.70 (1.02-2.84) and 1.36 (0.90-2.06).

Pack-years were examined as a combined measure of duration and dose of exposure to the husband's cigarette smoking. The odds ratios for all cell types of lung cancer combined and for adenocarcinoma of the lung are displayed in Fig. 1. Separate analyses were conducted with each control group for comparison. Because the findings were so similar for each group, the results are presented for the two control series combined ($n = 1131$). An increasing risk of lung cancer and adenocarcinoma of the lung associated with an increasing level of exposure to the spouse's cigarette smoking was found. The positive trend in risk by pack-years of exposure is statistically significant for adenocarcinoma of the lung ($P < 0.01$). A weaker dose response is observed when all histopathological types of lung cancer are combined (trend, $P = 0.07$).

Exposure to ETS from various sources during adult life was evaluated. The results are summarized in Table 6. For simplicity of presentation, the data in this table also represent the findings using the two control groups combined because the individual results using each control group were entirely consistent. Exposures to cigarette smoking from spouse(s), other household members, on the job and in other activities of adult life ("social") are each associated with an overall 40-60% significant elevation in the risk of adenocarcinoma of the lung. As noted previously for spouse-related exposures, the risk estimates for all lung cancers without regard to cell type tend to be slightly lower than the comparable estimates for adenocarcinoma of the lung. Significant positive trends ($P < 0.05$) in risk of adenocarcinoma of the lung were associated with increasing duration (years) of exposure to cigarette smoke from a spouse, other household members, and social occasions. For adult household exposures from a spouse and others, estimates of risk rose from lowest to highest in the 30 or more years of exposure category; however, trends were not smooth for exposures in occupational and social settings.

No association was found between risk of any type of lung cancer and childhood exposure to cigars, pipes, cigarettes, or all types of tobacco combined. Table 7 presents the estimated relative risks of lung cancer and adenocarcinoma of the lung among nonsmoking women whose father, mother, or other household member smoked during childhood. None differed significantly from unity. Years of exposure and amount smoked were also examined. No significant elevations in risk were found at any level of smoking by household members during childhood.

Discussion

One of the most striking findings of this study is the distribution of the histopathological cell types of lung cancer in a population-based series of cases well screened to determine lifetime nonsmoker status. Seventy-eight % of 359 reviewed eligible cases in this report were classified as adenocarcinomas. This high proportion of adenocarcinomas and the paucity of squamous and small cell carcinomas was consistent across all study

Table 5 Association between smoking status of spouse(s) and lung cancer risk^a: all lung cancer and adenocarcinoma of the lung

Spouse ever smoked tobacco (by type)	Cases	Colon cancer controls	Population controls	Adjusted odds ratio ^a	
				Colon cancer controls OR (95% CI)	Population controls OR (95% CI)
All lung carcinomas (n = 420)		(n = 351)	(n = 780)		
Any type of tobacco	294	231	492	1.28 (0.93-1.75)	1.29 (0.99-1.69)
Cigarettes	264	209	441	1.17 (0.87-1.59)	1.20 (0.93-1.55)
Cigars	64	54	97	1.14 (0.76-1.71)	1.26 (0.88-1.80)
Pipe	63	52	110	1.17 (0.78-1.77)	1.21 (0.85-1.72)
Adenocarcinoma (n = 281)		(n = 351)	(n = 780)		
Any type of tobacco	203	231	492	1.44 (1.01-2.05) ^b	1.47 (1.08-2.01) ^b
Cigarettes	184	209	441	1.31 (0.94-1.84)	1.36 (1.02-1.84) ^b
Cigars	41	54	97	1.05 (0.67-1.66)	1.15 (0.76-1.74)
Pipes	44	52	110	1.16 (0.74-1.82)	1.20 (0.81-1.79)

^a Adjusted for age (continuous), race (white, black, other), study area (Los Angeles, San Francisco Bay Area, Southern U.S.: Atlanta, Houston, and New Orleans), annual family income (<\$13,000, \$13,000-\$34,999, \$35,000+), and education (<high school degree, high school degree, some college or higher).

^b $P < 0.05$.

centers. In the study of Kabat and Wynder (8), a similar proportion (74%) of Kreyberg II type tumors was found in their series of 97 nonsmoking females whose self-reported nonsmoking status was confirmed by chart review. In the United States adenocarcinoma is the most common histopathological cell type of primary lung cancer in women, but the proportion of all female lung cancer cases with all subtypes of adenocarcinomas (papillary, acinar, bronchioloalveolar, and solid) is 34% (SEER Public User Tape, 1978-1987).

Our study, in which adenocarcinoma is predominant and is the cell type clearly associated with increased risk

from adult ETS exposures, is in contrast to several of the earlier studies of involuntary exposure to ETS. Trichopoulos *et al.* (2) in the initial case-control study of lung cancer and passive smoking among nonsmoking women excluded cases of adenocarcinoma including bronchioloalveolar; however, that study included no histopathological review. They reported an odds ratio from 1.8 to 3.4 associated with the husband's smoking habits. Dalgner *et al.* (16) reported a 3-fold elevated risk associated with the spouse's smoking only for squamous and small cell carcinomas and no increased risk of other cell types, of which adenocarcinoma and its subtype, bronchioloal-

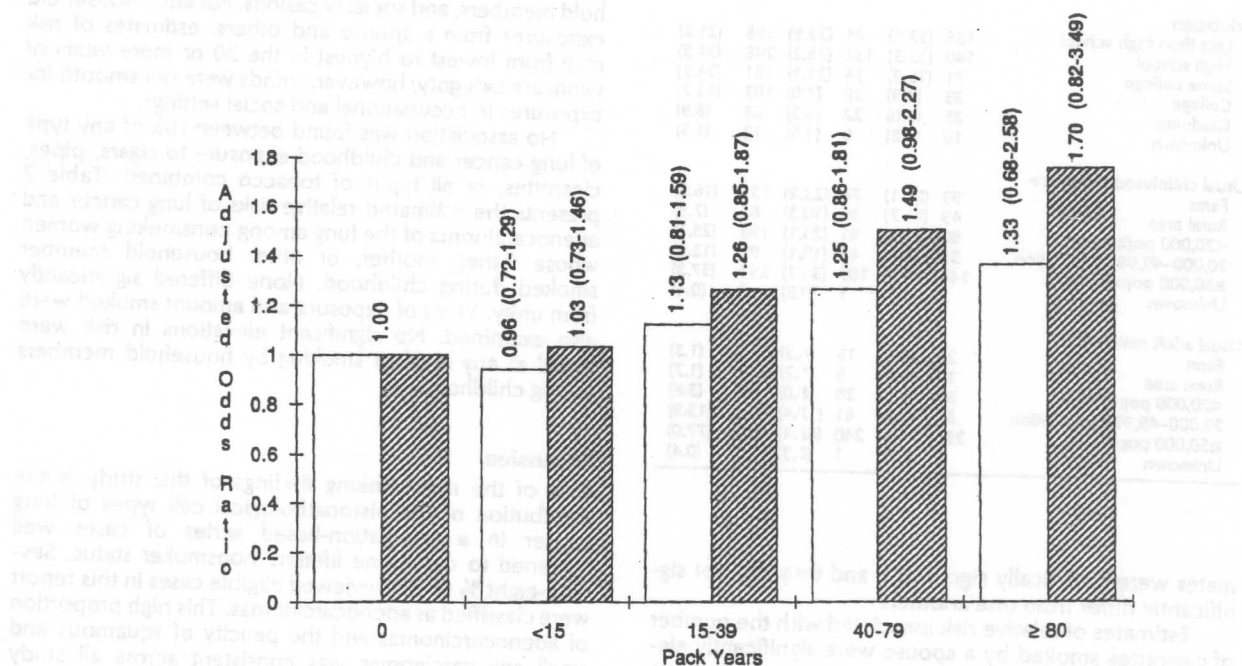


Fig. 1. Adjusted odds ratios for all lung cancer and for adenocarcinoma of the lung associated with pack-years of exposures from spouse(s). □, all lung cancer, trend $P = 0.07$; ▨, adenocarcinoma, trend $P < 0.01$.

Table 6 Association between risk^a of lung cancer and adult exposures to cigarette smoke among nonsmoking women

Years of exposure by source	All lung carcinomas adjusted odds ratio ^a (95% CI)	Adenocarcinoma of the lung adjusted odds ratio ^a (95% CI)
Household exposure		
Spouse		
Ever exposed ^b	1.21 (0.96–1.54)	1.38 (1.04–1.82) ^c
0 years	1.00	1.0
1–15	1.19 (0.88–1.61)	1.33 (0.93–1.89)
16–30	1.14 (0.82–1.59)	1.40 (0.96–2.05)
>30	1.25 (0.91–1.72)	1.43 (0.99–2.09)
	Trend <i>P</i> = 0.14	Trend <i>P</i> = 0.03
Other household members		
Ever exposed ^b	1.23 (0.97–1.56)	1.39 (1.05–1.82) ^c
0 years	1.00	1.00
1–5	1.20 (0.90–1.61)	1.36 (0.98–1.89)
6+ ^d	1.23 (0.89–1.69)	1.35 (0.93–1.94)
	Trend <i>P</i> = 0.12	Trend <i>P</i> = 0.04
Occupational exposure		
Ever exposed ^b	1.34 (1.03–1.73) ^c	1.44 (1.06–1.97) ^c
0 years	1.00	1.00
1–15	1.23 (0.86–1.77)	1.58 (1.05–2.39) ^c
16–30	1.45 (1.05–2.00) ^c	1.42 (0.97–2.07)
>30	1.30 (0.93–1.80)	1.37 (0.92–2.02)
	Trend <i>P</i> = 0.02	Trend <i>P</i> = 0.10
Social exposure^e		
Ever exposed ^b	1.58 (1.22–2.04) ^f	1.60 (1.19–2.14) ^f
0	1.00	1.00
1–15	1.34 (0.97–1.84)	1.29 (0.89–1.87)
16–30	2.01 (1.29–3.15) ^c	2.40 (1.47–3.90) ^f
>30	1.65 (0.98–2.80)	1.50 (0.78–2.77)
	Trend <i>P</i> = 0.0006	Trend <i>P</i> = 0.002

^a Adjusted for age, race, study area, annual income, and education.^b Referent: never exposed.^c *P* < 0.05.^d Too few subjects exposed 16+ years.^e Social exposure is defined as exposure of 2 or more h/week from sources other than occupational and household members, including spouse.^f *P* < 0.01.

veolar carcinoma, comprised 46.1% of the total female nonsmoking cases. In the Swedish study of Pershagen *et al.* (35), 57% of 77 female nonsmokers were adenocarcinomas and 31% squamous and small cell carcinomas. The only statistically significant ETS-associated increased risk was for squamous and small cell carcinomas, the cell types with the highest relative risks associated with active smoking. At the present time small numbers of squamous cell and small cell carcinomas in our data set preclude an adequate assessment of risk associated with ETS exposures for these cell types.

The findings of our study lend some support to the mechanism proposed by Wynder and Goodman (36) whereby inhalation of sidestream smoke might primarily increase risk of adenocarcinoma of the lung. They suggested that inhalation of sidestream smoke through the nasal passages would hinder deposition of respirable smoke particulates in the periphery of the lung while gaseous components such as volatile *N*-nitrosamines, formaldehyde, acetaldehyde, or nitrogen oxides, would

be likely to reach the deeper part of the lung. Both squamous cell and small cell carcinomas tend to be centrally located, rather than in the periphery of the lung.

Our study found statistically significant elevated risks of adenocarcinoma of the lung among female nonsmokers who had had household ETS exposure or ETS exposure in occupational settings or from other sources. Each of these exposures occurred during adulthood. Exposures during the first 18 years of life were consistently unrelated to the risk of lung cancer.

Any exposure (ever/never) from a spouse who smoked was associated with at least a 30% excess risk. Increasing amount per day and years smoked significantly increased risk. The pattern of risk was the same when cases were compared to colon cancer cases or population controls and was specific for adenocarcinoma of the lung. Findings for all lung cancers combined reflect the association between ETS and adenocarcinoma of the lung diluted by the weak association with other cell types.

The internal consistency of findings with the two control groups suggests that recall bias resulting from having a diagnosis of cancer is not a likely explanation of the observed effect. The possibility remains that nonsmoking lung cancer cases and nonsmoking colon cancer cases are not similarly motivated to remember exposures to the tobacco smoke of others.

The longest duration of exposure to ETS is associated with the greatest elevation in risk, 1.43, for exposure of 30 or more years to a husband's cigarette smoking. Although significant trends were found for other adult exposures, the dose response was not monotonic; relative risk estimates tended to decline in the longest exposure category. One possible explanation is that recall of quantitative measures of exposure is less reliable for exposures outside the home and for household members other than the spouse. A recent ten-country study was carried out by the International Agency for Research on Cancer designed to validate self-reported recent exposure of nonsmoking women to ETS from any source compared with the urinary concentration of cotinine. Duration of daily exposure to ETS from the husband was the strongest predictor of urinary cotinine (37). Studies by Pron *et al.* (38) and Coultas *et al.* (39) suggest that quantitative measures, particularly for exposures outside the home, are less reliable than categorical measures.

The lack of any association between childhood ETS exposures and lung cancer in our study, as well as the strong, consistent association with exposures during adulthood, contrasts with two recent reports by Janerich *et al.* (22) and Wu-Williams *et al.* (40). Differences in study design may contribute to the discrepant findings. About 25% (*n* = 45) of the 191 cases in the New York study were males, whereas our study was restricted to female cases (*n* = 420) (22). The authors report that there were only small differences between men and women in the amount of exposure to ETS measured by duration. The mean exposure of women to their husbands' tobacco smoke was 16.2 ± 16.7 years, while men had a mean exposure of 13.0 ± 17.0 years from smoking wives. Furthermore, there was a higher correlation between exposure from spouses lifetime ETS exposure for women in the study (*r* = 0.51) than for men (*r* = 0.37). Intensity (dose) of exposure and temporality of exposure from male and female smoker sources may differ considerably. Relatively small differences in dose, temporality, and

Table 7 Association between risk^a of lung cancer and childhood^b exposures to tobacco smoke among nonsmoking women

Ever smoked tobacco	Cases	Colon cancer controls	Population controls	Adjusted odds ratio ^a	
				Colon cancer controls OR (95% CI)	Population controls OR (95% CI)
All lung carcinomas					
Father	196	189	420	0.91 (0.67-1.24)	0.82 (0.64-1.07)
Mother	44	40	97	0.85 (0.53-1.38)	0.84 (0.56-1.26)
Other household member	177	152	327	0.83 (0.59-1.18)	0.96 (0.71-1.29)
Adenocarcinoma					
Father	139	189	420	0.96 (0.69-1.35)	0.89 (0.66-1.19)
Mother	30	40	97	0.91 (0.54-1.55)	0.89 (0.56-1.43)
Other household member	125	152	327	0.81 (0.55-1.20)	0.91 (0.64-1.29)

^a Adjusted for age, race, study area, annual income, and education.^b Childhood is defined as first 18 years of life.

duration in combination may yield more meaningful differences in exposure than that measured by duration alone. The inclusion of males in the New York study, with possibly lower doses of ETS exposure from smoking wives for fewer years and during a more recent time period, may have reduced the relative risk estimates that were not gender specific. A study in northeast China, which was comparable in size to our study, actually found a decreased risk of lung cancer associated with ETS exposures from spouses and a suggestive increased risk associated with paternal smoking (40). As suggested by the authors, these women had heavy exposures to both indoor and outdoor pollutants, which may have obscured any effect of ETS.

The studies which have examined childhood exposures are more limited than those which have focused on tobacco use by spouses, and the overall findings are inconclusive (3, 5, 11-14, 22, 41). Studies of the reliability of recall of ETS exposures suggest that recall of a parent's smoking history is less reliable than that for spouses (38, 39), and this may account in part for inconsistencies between studies. Janerich *et al.* (22) found a 2-fold increased risk associated with 25 or more smoker-years during childhood and adolescence but no increase for childhood exposures of less than 25 smoker-years (OR = 1.09). In most studies which have reported positive associations, the findings have been primarily for maternal ETS exposures in smokers rather than in nonsmokers. Correa *et al.* (5) found a significantly increased risk of lung cancer (OR = 1.36) among smokers whose mother smoked but no increased risk in nonsmokers and no elevated risk associated with the father's smoking. Wu *et al.* (14) reported a nonsignificantly elevated risk of adenocarcinoma of the lung (OR = 1.7) in females, 80% of whom had a history of smoking. Similarly, in a Swedish study of female lung cancer which included primarily smokers, a nonsignificantly elevated risk was associated with maternal (OR = 1.8) but not paternal (OR = 0.8) smoking (42). Other studies have failed to find an increased risk of lung cancer associated with childhood exposures (11, 12, 43). None of these studies examined maternal smoking as distinct from other childhood exposures. Childhood ETS exposures alone may be insufficient to increase lung cancer risk in lifetime nonsmokers but may increase risk in persons exposed transplacentally or during childhood who later smoke themselves (5).

The female lifetime nonsmokers with lung cancer in our study are considerably older than the female lung

cancer cases reported in the SEER program, most of whom have actively smoked. This may represent a cohort effect; that is, older women are less likely to have smoked. The age disparity might also reflect possible differences in response among active and passive smokers. The lower dose of ETS might require a longer duration of exposure for pulmonary carcinogenesis.

Although this report represents the findings of the first 3 years of a 5-year study, it is nevertheless the largest case-control study reported to date on this topic. The findings provide additional evidence in favor of a causal relationship between exposure to ETS and lung cancer in women who have never used tobacco themselves. A dose response, not likely due to chance, was apparent for exposure to tobacco smoke during adult life from a variety of exposure sources. The association was specific for both adenocarcinoma of the lung and for all lung cancers combined compared to colon cancer.

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