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The Relation of Passive Smoking to Lung Cancer[1]

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ABSTRACT

To evaluate the role of passive smoking in the development of lung cancer among nonsmokers, data were pooled from three large incident case-control interview studies. Ninety-nine lung cancer cases and 736 controls never used any form of tobacco. Overall the adjusted odds ratio for lung cancer among nonsmokers ever living with a smoker was 0.8 (95% confidence interval, 0.5–1.3) rising to 1.2 among those exposed for 40 or more years. Persons living with a spouse who smoked cigarettes were at increased risk (adjusted odds ratio, 1.5; 95% confidence interval, 0.8–2.8). When adjusted for age and gender, there was a significant trend in risk with increasing amounts smoked per week by the spouse (P = 0.05) and with cumulative pack-years of exposure (P = 0.03). This effect was limited to females, especially older women whose husbands were heavy smokers. The elevated risk associated with spouse smoking was restricted to squamous and small cell carcinomas (odds ratio, 2.9; 95% confidence interval, 0.9–9.3), which provides additional evidence linking passive smoking to lung cancer.

INTRODUCTION

The respiratory effects of passive smoking among nonsmokers are of increasing concern; evidence suggests that such exposure may increase the incidence of bronchitis and pneumonia in early life (1) and decrease lung function among nonsmoking adults (2). Recent attention has centered on the possible risk of lung cancer among nonsmokers exposed to environmental tobacco smoke (3–6), although epidemiological studies have been limited by the small number of cases available for analysis. The National Cancer Institute has recently collaborated on three large case-control interview studies of lung cancer which included questions about passive smoking. One of these studies, conducted in Louisiana, showed an increased risk of lung cancer among ever-married nonsmokers who had a spouse that smoked (6). To increase our sample size for study, data on nonsmokers from all three case-control studies were pooled and analyzed.

MATERIALS AND METHODS

Persons reporting that they had never used any tobacco products (cigarettes, pipe, cigars, snuff, or chewing tobacco) were selected from three case-control interview studies of lung cancer conducted in Louisiana, Texas, and New Jersey. The methods used in each of these studies have been reported previously (6–9). Because all three studies were designed in collaboration with the National Cancer Institute, they were similar in many respects, as shown in Table 1. Medical and pathology records were abstracted to determine the final diagnosis of each case. All were incident primary lung cancer cases diagnosed between 1976 and 1982, with nearly 100% histologically confirmed. Personal interviews were conducted with the study subject or, if the subject was deceased or too ill to respond, with a surrogate respondent. Except where noted, the questions asked in each of the study areas were very similar.

Details regarding the source and level of passive smoking exposures varied according to study area (Table 1). Texas provided the least specific data by ascertaining only if any member of the subject's household smoked while the subject was either a child or an adult and the total number of years of that exposure. New Jersey, on the other hand, inquired about the smoking habits of each household member during the subject's youth and adulthood. Louisiana requested information regarding the smoking patterns of spouse, mother, and father, but not other members of the household. An estimate of the potential underreporting of passive smoking exposure in Louisiana is provided by the New Jersey control group; 6% of the nonsmoking males reported passive smoking originating from household members other than spouse, mother, or father.

The final study population abstaining from tobacco consisted of 99 histologically confirmed lung cancer cases and 736 controls. This represented 1.2% of all male cases and 9.1% of all female cases in the original study populations, as compared to 15.0% of the male controls and 44.9% of the female controls. The final data file included all variables that could be standardized across the study areas.

Several potential confounders were examined, including gender, race, age, study area, respondent type (subject or next of kin), any self-reported chronic lung conditions, employment in suspected high-risk industries, asbestos exposure, carotene and total vitamin A intake, and whether parents had smoked. Due to the limitation imposed by small numbers, age was dichotomized into two age groups (<63 years and 63+ years). Logistic analyses utilizing three age groups did not substantially alter the adjusted odds ratios reported here. High-risk industries were those identified in a recent review of case-control studies of lung cancer (10) and included fishing, construction, lumber manufacturing, chemical and petroleum manufacturing, primary metal manufacturing, and shipbuilding. Nutrient indices were calculated from the food frequency questions for each study area, using nutrient content in a typical portion of each food (11, 12). Low intake was defined as the lowest quartile of intake for controls from each area. Because of the comparability problem resulting from the selective exclusion of persons diagnosed with chronic lung conditions in Louisiana, analyses were duplicated excluding all persons who reported having a chronic lung condition in all three study areas.

Statistical methods included the calculation of crude ORs[3] for lung cancer risks associated with passive smoking exposures. Because of the small numbers in this analysis, ORs were calculated using a 0.5 cell adjustment (13). Dose-response effects were examined using a stratified analysis and the Mantel-Haenszel test for trend (14). The logistic model was used to exclude the effects of potential confounders and to obtain maximum likelihood estimates of the adjusted ORs (15–17). Decisions concerning parameter deletions for the model were based on the t statistics for significance of the individual parameter estimates, on changes in the value of the log likelihood, and on the goodness-of-fit of the model as measured by the comparison of predicted to observed ORs, both stratified and crude. Maximum likelihood 95% CIs for the ORs were calculated from the logistic model (15) or from the stratified analysis (18).

RESULTS

The data from all three study areas were merged to examine the effect of any passive smoking exposure in the home envi-

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[3] The abbreviations used are: OR, odds ratio; CI, confidence interval.

Table 1 *Comparison of the three lung cancer case-control interview studies from which the nonusers of tobacco were selected*

	Study		
	Louisiana	Texas	New Jersey
Geographic area	29 Louisiana parishes	Gulf Coast of Texas	6 high-risk areas of New Jersey
Case diagnosis period	1979–1982	1976–1980	1980–1981
Study design	Hospital based	Population based	Population based
Racial groups included	Whites/blacks	Whites	Whites/blacks
Gender groups included	Males/females	Males/females	Males
Cooperation rate[a]			
Cases	91.8	91.5	87.7
Controls	93.5	87.9	73.4
No. of cases	1057 (M) 315 (F)	462 (M) 454 (F)	896 (M)
No. of controls	1073 (M) 320 (F)	451 (M) 464 (F)	1043 (M)
% histologically confirmed	97.8	100	100
Passive smoking data	Mother, father, spouse	Ever any household member	Specific household member
Nonusers of tobacco			
No. of cases	8 (M) 28 (F)	5 (M) 42 (F)	16 (M)
No. of controls	177 (M) 156 (F)	48 (M) 196 (F)	159 (M)

[a] $\frac{\text{No. of completed interviews} \times 100}{\text{No. of subjects contacted for interview}}$

ronment. There were slight variations in the passive smoking questions among the three study areas. However, since exposures from parents and spouse represented the bulk of passive smoking experienced by nonsmokers in the home, the decision to pool data on whether subjects had ever been exposed in the home environment appeared reasonable. There was no apparent increase in the risk of lung cancer among those who reported ever living with a household member who smoked (crude OR, 1.00; 95% CI, 0.64–1.56). Controlling for the strongest confounders (gender, age, and study area) reduced the OR to 0.84 (95% CI, 0.52–1.34). No significant differences were seen in the risks across sex and age strata or according to cell type of lung cancer.

A crude summary estimate of the duration of passive smoking exposure per individual was calculated for the Louisiana and New Jersey data by taking the maximum number of years that smoking was reported for mother or father and adding the years reported for spouse. In Texas, the reported value for years lived with any household member who smoked was used. In a stratified analysis, adjusted for age and gender, there was a slightly elevated OR of 1.24 (95% CI, 0.62–2.51) for those reporting 40 or more years of living with a smoker compared to 0.86 for <20 years and 0.82 for 20–39 years. These ORs were not significantly different from unity and showed no significant trend.

Since combining all known sources of passive smoking exposure might mask the effects of time period and intensity of exposure, the data were further analyzed with regard to specific sources of exposures. Because the Texas study lacked detailed data on the source and intensity of the passive smoking exposures, the remainder of the analysis was restricted to data on nonusers of tobacco from the Louisiana and New Jersey studies. The most complete information available for this combined population concerned the smoking patterns of the spouse. A total of 48 cases (22 males and 26 females) and 466 controls (318 males and 148 females) were ever-married nonusers of tobacco. The crude OR for lung cancer associated with exposure to a smoking spouse was 1.87 (95% CI, 1.03–3.42) (Table 2). Adjusting for confounding by gender, age, and study area reduced the odds ratio to 1.47. When controlling for age and gender, a significant upward trend was seen for increasing amount smoked per week by the spouse ($P = 0.05$) and cumulative pack-years of exposure ($P = 0.03$). Duration of spouse smoking, independent of amount, showed no consistent pattern.

Sex differences in risk were observed, with adjusted ORs of 1.96 for females (95% CI, 0.82–4.70) and 0.93 for males (95% CI, 0.30–2.90). This appears to reflect the greater frequency and amount smoked by the husbands of nonsmoking women compared to the wives of nonsmoking men. In the control series, women were much more likely than men to have a spouse who smoked (48.0% compared to 18.2%), and the average exposure originating from the smoking spouse was greater for women than for men (mean pack-years, 40.6 for women and 27.1 for men). The greatest risk was seen among older women (63+ years) whose husbands smoked at the highest intensity level (280 or more cigarettes/week) (OR, 5.14; 95% CI, 1.40–18.95). A dose-response relationship ($P = 0.02$) occurred among females with increasing pack-years of exposure from spouse smoking, with ORs ranging up to 2.99 (95% CI, 0.96–9.37) for females with greater than 35 pack-years of exposure. The majority of nonsmoking males had 20–35 pack-years of exposure. Despite a suggestion of increased risk for men in this category (OR, 2.48; 95% CI, 0.52–10.23), the numbers were small, and no dose response was detected.

Table 2 *Odds ratios for lung cancer associated with a spouse smoking exposure among ever-married nonusers of tobacco in Louisiana and New Jersey*

Total			
Cases	Controls	Crude OR	Adjusted OR[a]
48	466	1.87 (1.03–3.42)	1.47 (0.76–2.83)
Amount spouse smoked/wk			
<140 cigarettes			1.36 (0.41–4.21)
140–279 cigarettes			1.31 (0.48–3.47)
280+ cigarettes			2.71 (0.84–8.52)
Significant trend ($P = 0.05$) for amount smoked			
Duration of spouse smoking exposure			
1–20 yr			1.73 (0.52–5.42)
21–30 yr			1.78 (0.60–5.10)
>30 yr			1.24 (0.42–3.53)
Pack-yr of exposure			
<20 pack-yr			0.78 (0.17–3.03)
20–35 pack-yr			1.90 (0.56–6.07)
>35 pack-yr			2.15 (0.84–5.40)
Significant trend ($P = 0.03$) for pack-yr of exposure			

[a] Overall OR (1.47) adjusted for gender, age, and study area in the logistic model (15–17); all other ORs adjusted for gender and age (18).

The ORs for lung cancer among nonsmokers were examined for the following histological types: adenocarcinoma; squamous and small cell carcinomas; and other cell types which included bronchioalveolar, undifferentiated, mixed, and not otherwise specified carcinomas, as well as carcinoids. As shown in Table 3, adenocarcinoma accounted for approximately one-third of the lung cancers in both sexes combined. A larger proportion

Table 3 *Cell type distribution of lung cancer among ever-married nonusers of tobacco by sex*

Cell type	Male		Female	
	No.	%	No.	%
Adenocarcinoma	7	31.8	9	34.6
Squamous and small cell carcinoma	9	40.9	5	19.2
Other	6	27.3	12	46.2
Bronchioalveolar carcinoma	2	9.1	3	11.5
Undifferentiated	2	9.1	3	11.5
Mixed	0	0	1	3.8
Not otherwise specified carcinoma	2	9.1	3	11.5
Carcinoid	0	0	2	7.7

Table 4 *Cell type-specific ORs for lung cancer associated with spouse smoking exposure among ever-married, nonusers of tobacco in Louisiana and New Jersey*

Cell type	Total		Crude OR	Adjusted OR[a]
	Cases	Controls		
Adenocarcinoma	16	466	1.25 (0.44–3.51)	1.02 (0.33–3.16)
Squamous and small cell carcinoma	14	466	2.61 (0.93–7.32)	2.88 (0.91–9.10)
Other	18	466	2.11 (0.84–5.33)	1.31 (0.48–3.57)

[a] Logistic model included gender, age, and study area as potential confounders (15–17).

of squamous and small cell carcinomas was seen for men than for women, while other types of lung cancer were more common in women than men. The adjusted ORs (Table 4) associated with exposure to a smoking spouse varied from 1.02 for adenocarcinoma to 2.88 for squamous and small cell carcinomas.

The elevated risk for the squamous and small cell category was due mainly to the female cases in Louisiana; all five of the nonsmoking women with these cell types had spouses who smoked. The spouses of four of these five women smoked at a level greater than 25 pack-years. The men whose wives smoked showed a moderate increase in risk for squamous and small cell carcinomas (crude OR, 1.48; 95% CI, 0.34–6.39). Exclusion of all subjects who reported having a chronic lung condition did not alter the risk patterns.

Except for gender, age, and study area, no confounding was detected. The increased risks for lung cancer associated with passive smoking were not accounted for by race, respondent type, any self-reported chronic lung condition, employment in a high-risk industry, asbestos exposure, total vitamin A or carotene intake, or smoking by the parents. When the referent group was restricted to those persons reporting no passive smoking exposure from either a spouse or parent, the patterns of risk remained consistent with those we have presented.

DISCUSSION

The analysis of pooled data from three case-control studies in the United States suggested an increased risk of lung cancer among nonusers of tobacco who were married to smokers. Among women this risk appeared to be dependent on the intensity of exposure to environmental tobacco smoke as estimated by the amount smoked by their husbands. Small numbers and relatively low exposures made it difficult to assess the role of passive smoking among tobacco-abstaining men whose wives smoked. While the overall ORs were not statistically significant, the finding of a dose-dependent risk of lung cancer among nonsmoking women is consistent with other observations in the literature. Hirayama (3) in Japan and Trichopoulos *et al.* (4) in Greece reported a significant increase in the lung cancer risk of nonsmoking women whose spouses smoked. Subsequently, the prospective survey of the American Cancer Society (5) found an elevated risk for passive smoking among nonsmoking women although the excess was nonsignificant and lacked a dose-response relationship. In our study the risk of lung cancer was not increased when passive smoking exposures from childhood and adulthood were examined collectively, emphasizing the need to obtain source-specific exposure data.

When the lung cancers were analyzed by cell type, the increased risk associated with passive smoking appeared restricted to squamous and small cell carcinomas, the types most closely linked to active smoking (19). This pattern suggests that passive smoking may contribute to the risk of lung cancer through mechanisms similar to those of active smoking, although sidestream smoke contains higher concentrations of certain compounds, such as nitrosamines, compared to mainstream smoke (20). In a recent case-control study by Garfinkel *et al.* (21), significant risks for both squamous cell carcinoma and adenocarcinoma were observed among nonsmoking women exposed to a spouse smoking at home, with the risks for squamous cell cancer being 3 times greater than for adenocarcinoma. Among nonsmoking Chinese women in Hong Kong, Koo *et al.* (22) found that the risk of passive smoking was greater for squamous and small cell cancers than for adenocarcinomas.

Although our analyses included nonsmokers from three large series of lung cancer, the small number of cases still precluded any definitive answers on the carcinogenic effects of passive smoking. Other limitations concern the difficulty in quantifying exposures from passive smoking derived from interview data and in detecting relatively low-level effects. Since our study was based on questionnaires, it was not possible to evaluate certain other exposures (*e.g.*, indoor radon daughter products) that may affect the risk of lung cancer among nonsmokers.

Our study was also limited by the assessment of passive smoking exposures experienced only in the home environment and by the use of a relatively crude measure of exposure. We assumed for this analysis that the amount and duration of a spouse's smoking habit approximated the passive smoking exposure realized by an individual at home. Fuller characterization of passive smoking should address the intensity of exposure, a function of the amount of time spent in close proximity to a smoker as well as the amount that individual smokes. In our study, the sex differences observed in exposure and risk suggest the desirability of continuing to focus attention on the nonsmoking wives of smokers, while encouraging the collection of data on workplace and other nonhousehold exposures to ambient tobacco smoke.

Whenever possible, future epidemiological studies should incorporate laboratory measurements of tobacco smoke constituents and by-products such as cotinine, the major metabolite of nicotine detected in body fluids. Among nonsmokers, a dose-response relationship has been observed between the levels of urinary cotinine and self-reported exposure to passive smoking (23, 24). Thus, while the available epidemiological data on nonsmokers suggest that passive smoking increases the risk of lung cancer, mainly of the squamous and small cell types, confirmation will probably require larger study sizes as well as more extensive and innovative assessment of exposure to environmental tobacco smoke.

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