Short Communication

Cancer Epidemiology, Biomarkers & Prevention

Secondhand Tobacco Smoke Exposure and Lung Adenocarcinoma *In Situ*/Minimally Invasive Adenocarcinoma (AIS/MIA)

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Abstract

The aim of this study was to estimate the effect of exposure to secondhand tobacco smoke on the incidence of lung adenocarcinoma *in situ*/minimally invasive adenocarcinoma (AIS/MIA). Data from seven case–control studies participating in the International Lung Cancer Consortium (ILCCO) were pooled, resulting in 625 cases of AIS/MIA and 7,403 controls, of whom 170 cases and 3,035 controls were never smokers. Unconditional logistic regression was used to estimate adjusted ORs (OR_{adj}) and 95% confidence intervals (CI), controlling for age, sex, race, smoking status (ever/never), and pack-years of smoking. Study center was included in the models as a random-effects intercept term. Ever versus never exposure to secondhand tobacco smoke was positively associated with AIS/MIA incidence in all subjects ($OR_{adj} = 1.48$; 95% CI, 1.14–1.93) and in never smokers ($OR_{adj} = 1.45$; 95% CI, 1.00–2.12). There was, however, appreciable heterogeneity of OR_{adj} across studies ($P = 0.01$), and the pooled estimates were largely influenced by one large study (40% of all cases and 30% of all controls). These findings provide weak evidence for an effect of secondhand tobacco smoke exposure on AIS/MIA incidence. Further studies are needed to assess the impact of secondhand tobacco smoke exposure using the newly recommended classification of subtypes of lung adenocarcinoma. *Cancer Epidemiol Biomarkers Prev; 24(12); 1902–6. ©2015 AACR.*

Introduction

In 2011, the multidisciplinary team of the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society recommended replacing the bronchioloalveolar carcinoma (BAC) classification with adenocarcinoma *in situ* (AIS) and minimally invasive adenocarcinoma (MIA), due to the wide spectrum of clinical and histologic characteristics within BAC (1). AIS/MIA has distinct molecular, pathologic, clinical, and epidemiologic features (2–6). Similar to other types of lung cancer, AIS/MIA is positively associated with tobacco smoking (7–11). However, the estimated effect of tobacco smoking is weaker for AIS/MIA than for other types of lung cancer, including other types of adenocarcinoma (6, 11, 12).

To the best of our knowledge, the study by Bracci and colleagues (10) is the only published report on the association between secondhand tobacco smoke exposure and AIS/MIA. In that study, secondhand tobacco smoke exposure in ever smokers and never smokers combined was not found to be associated with AIS ($OR_{adj} = 0.95$; 95% confidence intervals; CI, 0.57–1.6 and $OR_{adj} = 1.1$; 95% CI, 0.60–2.1 among whites and non-whites, respectively). However, the analysis included only 95 cases among never smokers. The aim of the present analysis is to assess the association between secondhand tobacco smoke exposure and AIS/MIA using a larger, pooled dataset.

Materials and Methods

We pooled data from seven case–control studies participating in the International Lung Cancer Consortium (ILCCO). All studies with data on secondhand tobacco smoke exposure and at least five cases of AIS/MIA among never smokers were included in the analysis. These cancers were classified as BAC in the original

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Table 1. Characteristics of lung AIS/MIA cases and controls by tobacco smoking status

	All		Never smokers	
	Cases, *n* (%)	**Controls, *n* (%)**	**Cases, *n* (%)**	**Controls, *n* (%)**
Total	625	7,403	170	3,035
Study (reference)				
Mayo Clinic (13, 14)	247 (39.5)	2,235 (30.2)	67 (39.4)	812 (26.8)
Harvard University (15)	196 (31.4)	1,513 (20.4)	28 (16.5)	479 (15.8)
Family Health Study (FHS; 16, 17)	32 (5.1)	912 (12.3)	24 (14.1)	534 (17.6)
University of California at Los Angeles (UCLA; 18)	39 (6.2)	1,038 (14.0)	18 (10.6)	470 (15.5)
Women's Epidemiology of Lung Disease (WELD; 19)	59 (9.4)	567 (7.7)	16 (9.4)	279 (9.2)
University of Hawaii (20)	38 (6.1)	587 (7.9)	12 (7.1)	224 (7.4)
Cancer of the Respiratory Tract Biorepository (CREST; 21)	14 (2.2)	551 (7.4)	5 (2.9)	237 (7.8)
Age (years)				
Less than 50	65 (10.4)	1,940 (26.2)	28 (16.5)	918 (30.2)
50–59	117 (18.7)	1,836 (24.8)	28 (16.5)	713 (23.5)
60–69	213 (34.1)	1,846 (24.9)	49 (28.8)	647 (21.2)
70 or above	230 (36.8)	1,781 (24.1)	65 (38.2)	757 (24.9)
Sex				
Male	215 (34.4)	3,607 (48.7)	37 (21.8)	1,125 (37.1)
Female	410 (65.6)	3,796 (51.3)	133 (78.2)	1,910 (62.9)
Race/ethnicity				
White	540 (86.4)	6,123 (82.7)	131 (77.1)	2,428 (80.0)
Asian	30 (4.8)	328 (4.4)	16 (9.4)	164 (5.4)
Hispanic/Latino	10 (1.6)	224 (3.0)	8 (4.7)	100 (3.3)
Black	24 (3.8)	502 (6.8)	7 (4.1)	243 (8.0)
Other	21 (3.4)	226 (3.1)	8 (4.7)	100 (3.3)
Tobacco smoking				
Never	170 (27.2)	3,035 (41.0)		
Ever	455 (72.8)	4,368 (59.0)		
Exposure to secondhand tobacco smoke				
Never	74 (11.8)	1,520 (20.5)	39 (22.9)	880 (29.0)
Ever	551 (88.2)	5,883 (79.5)	131 (77.1)	2,155 (71.0)

studies because the studies were conducted when the new classification was not yet in place. Details of each study have been reported previously (13–21). Each study used a structured questionnaire to collect epidemiologic data, including exposure to secondhand tobacco smoke at home and the workplace. There were some variations in the wording of the questions regarding exposure to secondhand smoke. For example, the Mayo Clinic study asked, "Were/are you regularly exposed to environmental (second-hand) cigarette smoke (from father, mother, or spouse)?" whereas the Harvard Study asked, "How often does someone smoke inside your home?" Other information included secondhand smoke exposure duration, intensity, and childhood exposure history. The pooled data consisted of 625 cases of AIS/MIA, of whom 170 were never smokers, and 7,403 controls, of whom 3,035 were never smokers.

Unconditional logistic regression was used to estimate OR and 95% CIs for the association between secondhand tobacco smoke exposure and the incidence of AIS/MIA. In order to mitigate sparse-data bias when estimating study-specific associations, we used the semi-Bayes method with a null-effect prior OR = 1 (95% CI, 0.25–4.00) for the effect of secondhand smoke on AIS/MIA incidence (22, 23). In addition to secondhand tobacco smoke exposure status (ever vs. never), we examined exposure location, duration, and childhood exposure status as predictors of AIS/MIA incidence. All models were adjusted for age (less than 50, 50–59, 60–69, or 70 years and above), sex, and race/ethnicity (non-Hispanic white, Asian, Hispanic/Latino, African American/black, or other). When examining ever smokers and never smokers combined, we also adjusted for tobacco smoking status (ever vs. never) and pack-years of smoking. To control for heterogeneity of effects across studies, study was included as a random effects intercept term in all models. We carried out stratified analyses by age (<65 years old vs. ≥65 years old) and sex. Stratification by race was not possible due to the limited sample sizes of non-whites. We used Cochran's Q test to assess heterogeneity of ORs across studies, age, and sex. All statistical analyses were performed using SAS 9.4.

Results

The distributions of demographic characteristics and tobacco exposure status of the cases and controls are presented in Table 1. The cases were more likely than the controls to be 60 years old or above, female, white non-Hispanic, ever smokers, and ever exposed to secondhand tobacco smoke. The OR_{adj} for the estimated effect of tobacco smoking was 1.97 (95% CI, 1.62–2.39; results not shown).

Study-specific associations between secondhand smoke exposure and AIS/MIA incidence are presented in Table 2. Most of the studies lacked sufficient numbers of unexposed cases to produce stable estimates on their own. There was evidence of heterogeneity of effects across studies ($P = 0.01$ and $P = 0.005$ in the total sample and never smokers, respectively).

In the pooled analysis, exposure to secondhand tobacco smoke was associated with AIS/MIA with adjusted ORs of 1.48 (95% CI, 1.14–1.93) in the total sample and 1.45 (95% CI, 1.00–2.12) in never smokers (Table 3). When we excluded the largest study (by Mayo Clinic), the OR_{adj} was reduced to 1.30 (0.87–1.95) in the total sample and 1.21 (95% CI, 0.68–2.15) in never smokers (results not shown). The association between secondhand tobacco smoke and AIS/MIA in all subjects differed little by sex ($P = 0.79$) or age ($P = 0.10$),

Table 2. Study-specific associations between secondhand tobacco smoke exposure and lung AIS/MIA by tobacco smoking status

	All			Never smokers		
Ever exposed to secondhand smoke	**Cases, *n***	**Controls, *n***	**OR[a] (95% PLL)**	**Cases, *n***	**Controls, *n***	**OR[b] (95% PLL)**
Mayo Clinic						
Never exposed	47	721	1 (reference)	21	386	1 (reference)
Ever exposed	200	1,514	1.68 (1.22–2.37)	46	426	1.70 (1.04–2.84)
Harvard University						
Never exposed	4	54	1 (reference)	1	20	1 (reference)
Ever exposed	192	1,459	1.41 (0.65–3.33)	27	459	0.91 (0.31–3.16)
FHS[c]						
Never exposed	0	76	1 (reference)	0	71	1 (reference)
Ever exposed	32	836	2.66 (1.01–7.85)	24	463	2.67 (1.01–7.90)
UCLA[d]						
Never exposed	14	307	1 (reference)	11	199	1 (reference)
Ever exposed	25	731	0.67 (0.34–1.41)	7	271	0.59 (0.25–1.35)
WELD[e]						
Never exposed	5	76	1 (reference)	4	53	1 (reference)
Ever exposed	54	491	1.30 (0.60–3.12)	12	226	0.91 (0.35–2.52)
University of Hawaii						
Never exposed	3	45	1 (reference)	2	32	1 (reference)
Ever exposed	35	542	0.98 (0.40–2.64)	10	192	0.95 (0.34–2.87)
CREST[f]						
Never exposed	1	241	1 (reference)	0	119	1 (reference)
Ever exposed	13	310	2.56 (1.02–6.98)	5	118	2.04 (0.67–6.58)
$P_{heterogeneity}$ across studies			*0.010*			*0.005*

[a]ORs are adjusted for age, sex, race/ethnicity, tobacco smoking status (ever/never), and pack-years of smoking. PLL: profile-likelihood limits.
[b]ORs are adjusted for age, sex, and race/ethnicity.
[c]FHS: Family Health Study.
[d]UCLA: University of California at Los Angeles.
[e]WELD: Women's Epidemiology of Lung Disease.
[f]CREST: Cancer of the Respiratory Tract Biorepository.

although the magnitude of association was greater in the ≥65 years age group (OR_{adj} = 1.79; 95% CI, 1.09–2.96 in never smokers) than in the <65 years group (OR_{adj} = 1.30; 95% CI, 0.78–2.14 in never smokers). Exposure location, duration, and childhood exposure were inconsistently associated with AIS/MIA (Supplementary Table S1).

Discussion

This is the largest analysis examining the relationship between exposure to secondhand tobacco smoke and AIS/MIA. Contrary to the null associations reported in the study by Bracci and colleagues (10), our results provide weak evidence that exposure to secondhand tobacco smoke increases the risk of AIS/MIA.

However, our results must be interpreted with caution since there were several limitations in the present analysis. First, there was appreciable heterogeneity across studies, possibly due to varying degrees of misclassification of the exposure status. The positive association observed when all seven studies were pooled was largely reduced after the Mayo Clinic study was excluded from the analysis. The number of AIS/MIA cases was not sufficient to yield precise estimates of associations among never smokers or in stratified analyses. We did not observe

Table 3. Associations between exposure to secondhand tobacco smoke and lung AIS/MIA by tobacco smoking status

	All			Never smokers		
Ever exposed to secondhand smoke	**Cases, *n***	**Controls, *n***	**OR[a] (95% CI)**	**Cases, *n***	**Controls, *n***	**OR[b] (95% CI)**
All						
Never exposed	74	1,520	1 (reference)	39	880	1 (reference)
Ever exposed	551	5,883	1.48 (1.14–1.93)	131	2,155	1.45 (1.00–2.12)
Females						
Never exposed	48	723	1 (reference)	30	523	1 (reference)
Ever exposed	362	3,073	1.41 (1.02–1.95)	103	1,387	1.37 (0.89–2.10)
Males						
Never exposed	26	797	1 (reference)	9	357	1 (reference)
Ever exposed	189	2,810	1.61 (1.06–2.44)	28	768	1.47 (0.74–2.91)
<65 years old						
Never exposed	38	937	1 (reference)	24	560	1 (reference)
Ever exposed	237	3,697	1.41 (0.98–2.04)	52	1,337	1.30 (0.78–2.14)
≥65 years old						
Never exposed	36	583	1 (reference)	15	320	1 (reference)
Ever exposed	314	2,186	1.64 (1.15–2.35)	79	818	1.79 (1.09–2.96)

[a]ORs are adjusted for age (except for age-specific estimates), sex (except for the sex-specific estimates), race/ethnicity, tobacco smoking status, and pack-years of smoking.
[b]ORs are adjusted for age (except for age-specific estimates), sex (except for the sex-specific estimates), and race/ethnicity.

monotonic associations between duration of secondhand smoke exposure and AIS/MIA, which may have been due to the limited sample size or misclassification of exposure duration. Information about the intensity of exposure to secondhand smoke was not available for most of the studies. Furthermore, there may have been uncontrolled residual confounding by other risk factors such as occupational exposures, family history of cancer, and diet.

A number of previous studies have investigated the associations between secondhand tobacco smoke exposure and the major histologic subtypes of lung cancer. In a recent pooled analysis of the ILCCO, the adjusted ORs for the association between secondhand smoke exposure and lung cancer among never smokers were 1.26 (95% CI, 1.10–1.44) for adenocarcinoma, 1.41 (95% CI, 0.99–1.99) for squamous cell carcinoma, 1.48 (95% CI, 0.89–2.45) for large cell carcinoma, and 3.09 (95% CI, 1.62–5.89) for small cell carcinoma (24). These results—especially that of adenocarcinoma—were comparable with those reported in previous meta-analyses by Hackshaw and colleagues (RR = 1.25; 95% CI, 1.07–1.46 for adenocarcinoma and RR = 1.58; 95% CI, 1.14–2.19 for squamous and small cell carcinomas combined) and by Boffetta (RR = 1.29; 95% CI, 1.15–1.37 for adenocarcinoma, RR = 1.38; 95% CI, 0.87–2.20 for squamous cell carcinoma, and RR = 1.47; 95% CI, 0.84–2.56 for small cell carcinoma; ref. 25, 26).

The international multidisciplinary classification for lung adenocarcinoma was developed to provide an integrated approach to classification "that will help to define categories that have distinct clinical, radiologic, molecular, and pathologic characteristics" (1). This improved classification may also lead to a better understanding of risk factors for lung adenocarcinoma subtypes. Exposure to secondhand tobacco smoke might be a risk factor for adenocarcinoma subtypes formerly classified as BAC. Future studies should continue to examine specific subtypes of adenocarcinoma with regard to their association with first- and second-hand tobacco smoke.

Disclosure of Potential Conflicts of Interest

P. Boffetta is a consultant/advisory board member for the FDA. No potential conflicts of interest were disclosed by the other authors.

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