HHS Public Access

Author manuscript

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2016 December 01.

Published in final edited form as:

Cancer Epidemiol Biomarkers Prev. 2015 December ; 24(12): 1902–1906. doi: 10.1158/1055-9965.EPI-15-0436.

Secondhand tobacco smoke exposure and lung adenocarcinoma in situ/minimally invasive adenocarcinoma (AIS/MIA)

Claire H. Kim[1], **Yuan-Chin Amy Lee**[2], **Rayjean J. Hung**[3], **Paolo Boffetta**[4], **Dong Xie**[5,6], **Jason A. Wampfler**[6], **Michele L. Cote**[7], **Shen-Chih Chang**[1], **Donatella Ugolini**[8,9], **Monica Neri**[10], **Loic Le Marchand**[11], **Ann G. Schwartz**[7], **Hal Morgenstern**[12], **David C. Christiani**[13], **Ping Yang**[6], and **Zuo-Feng Zhang**[1]

[1]Department of Epidemiology, Fielding School of Public Health, University of California at Los Angeles (UCLA), Los Angeles, CA

[2]Department of Family and Preventive Medicine, University of Utah, Salt Lake City, UT

[3]Lunenfeld-Tanenbaum Research Institute of Mount Sinai Hospital, Toronto, Canada

[4]The Tisch Cancer Institute and Institute for Translational Epidemiology, Icahn School of Medicine at Mount Sinai, New York, NY

[5]Department of Thoracic Surgery, ShangHai Pulmonary Hospital

[6]Mayo Clinic Cancer Center, Rochester, MN, USA

[7]Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI, USA

[8]Internal Medicine, University of Genoa, Genoa, Italy

[9]Unit of Epidemiology, Biostatistics and Clinical Trials, IRCSS Azienda Ospedaliera Universitaria San Martino-IST-Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy

[10]Clinical and Molecular Epidemiology, IRCCS San Raffaele Pisana, Rome, Italy

[11]Cancer Epidemiology Program, University of Hawaii Cancer Center, Honolulu, HI

[12]Departments of Epidemiology and Environmental Health Sciences, School of Public Health, and Comprehensive Cancer Center, University of Michigan, Ann Arbor, MI, USA

[13]Department of Environmental Health, Harvard University School of Public Health, Boston, MA

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 7 case-controls studies participating in the International Lung Cancer Consortium (ILCCO)

CORRESPONDING AUTHOR, Zuo-Feng Zhang, M.D., Ph.D., Department of Epidemiology, Fielding School of Public Health, University of California at Los Angeles (UCLA), 71-225 CHS, Box 951772, 650 Charles E Young Drive, South, Los Angeles, CA, 90095-1772, USA; Phone: 310-825-8418; Fax: 310-206-6039; zfzhang@ucla.edu.

CONFLICT OF INTEREST

P. Boffetta was consultant to the FDA on tobacco-related cancer. No potential conflicts of interest were disclosed by the other authors.

were pooled, resulting in 625 cases of AIS/MIA and 7,403 controls, of whom 170 cases and 3,035 controls were never smokers. Semi-Bayes logistic regression was employed to estimate adjusted odds ratios (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 vs. 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.

Keywords

lung cancer; bronchioloalveolar carcinoma; adenocarcinoma in situ; minimally invasive adenocarcinoma; secondhand tobacco smoke; environmental tobacco smoke; passive smoking

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 et al. [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% CI 0.57-1.6 and OR_{adj}=1.1; 95% CI 0.60-2.1 among whites and nonwhites, 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 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 odds ratios (OR) and 95% confidence intervals (CI) for the association between secondhand tobacco smoke exposure and the incidence of AIS/MIA. In order to mitigate sparse-data bias, we used the semi-Bayes method with a null-effect prior OR=1 (95% interval 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), 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 et al. [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 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 regarding 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 histological 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 to those reported in previous meta-analyses by Hackshaw et al. (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) [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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

FINANCIAL SUPPORT

The FHS and WELD studies were supported by the Karmanos Cancer Institute and the National Institutes of Health (R01CA060691, R01CA87895, N01-PC35145, P30CA22453, and K07CA125203 to A.G. Schwartz). The UCLA study was supported by the National Institutes of Health (DA11386, ES011667, and CA90833 to Z.F. Zhang; CA09142 to C.H. Kim) and Alper Research funds for Environmental Genomics (to Z.F. Zhang). The Harvard study was supported by the National Institutes of Health (CA092824, CA74386 and CA090578 to D. Christiani). The Mayo Clinic (MAYO) studies were supported by the Mayo Foundation Fund and the National Institutes of Health (CA77118, CA80127, CA115857, and CA084354 to P. Yang). The Hawaii study was supported by the National Institutes of Health (R01CA 55874 to L. Le Marchand). The CREST study was supported by the University of Genoa and Associazione Italiana per la Ricerca sul Cancro (AIRC; to M. Neri). The ILCCO data management was supported by Cancer Care Ontario Research Chair of Population Studies (to R. J. Hung).

REFERENCES

1. Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, Yatabe Y, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol. 2011; 6:244–285. [PubMed: 21252716]
2. Koga T, Hashimoto S, Sugio K, Yoshino I, Mojtahedzadeh S, Matsuo Y, et al. Clinicopathological and molecular evidence indicating the independence of bronchioloalveolar components from other subtypes of human peripheral lung adenocarcinoma. Clin Cancer Res. 2001; 7:1730–1738. [PubMed: 11410513]
3. Read WL, Page NC, Tierney RM, Piccirillo JF, Govindan R. The epidemiology of bronchioloalveolar carcinoma over the past two decades: analysis of the SEER database. Lung Cancer. 2004; 45:137–142. [PubMed: 15246183]
4. Raz DJ, He B, Rosell R, Jablons DM. Bronchioloalveolar carcinoma: a review. Clin Lung Cancer. 2006; 7:313–322. [PubMed: 16640802]
5. Arenberg D. American College of Chest Physicians. Bronchioloalveolar lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest. 2007; 132:306S–313S. [PubMed: 17873176]
6. Grover FL, Piantadosi S. Recurrence and survival following resection of bronchioloalveolar carcinoma of the lung—The Lung Cancer Study Group experience. Ann Surg. 1989; 209:779–790. [PubMed: 2543339]
7. Morabia A, Wynder EL. Cigarette smoking and lung cancer cell types. Cancer. 1991; 68:2074–2078. [PubMed: 1655236]
8. Falk RT, Pickle LW, Fontham ET, Greenberg SD, Jacobs HL, Correa P, et al. Epidemiology of bronchioloalveolar carcinoma. Cancer Epidemiol Biomarkers Prev. 1992; 1:339–344. [PubMed: 1339048]
9. Boffetta P, Jayaprakash V, Yang P, Asomaning K, Muscat JE, Schwartz AG, et al. Tobacco smoking as a risk factor of bronchioloalveolar carcinoma of the lung: pooled analysis of seven case-control studies in the International Lung Cancer Consortium (ILCCO). Cancer Causes Control. 2011; 22:73–79. [PubMed: 21072579]
10. Bracci PM, Sison J, Hansen H, Walsh KM, Quesenberry CP, Raz DJ, et al. Cigarette smoking associated with lung adenocarcinoma in situ in a large case-control study (SFBALCS). J Thorac Oncol. 2012; 7:1352–1360. [PubMed: 22814813]
11. Tran HN, Li Y, Siu S, Baer D, Friedman GD, Udaltsova N, et al. Predictors of lung cancer: noteworthy cell type differences. Perm J. 2013; 17:23–29. [PubMed: 23704839]

12. Barsky SH, Cameron R, Osann KE, Tomita D, Holmes EC. Rising incidence of bronchioloalveolar lung carcinoma and its unique clinicopathologic features. Cancer. 1994; 73:1163–1170. [PubMed: 8313318]
13. Yang P, Sun Z, Krowka MJ, Aubry MC, Bamlet WR, Wampfler JA, et al. Alpha1-antitrypsin deficiency carriers, tobacco smoke, chronic obstructive pulmonary disease, and lung cancer risk. Arch Intern Med. 2008; 168:1097–1103. [PubMed: 18504338]
14. de Andrade M, Ebbert JO, Wampfler JA, Miller DL, Marks RS, Croghan GA, et al. Environmental tobacco smoke exposure in women with lung cancer. Lung Cancer. 2004; 43:127–134. [PubMed: 14739032]
15. Xu LL, Wain JC, Miller DP, Thurston SW, Su L, Lynch TJ, et al. The NAD(P)H:quinone oxidoreductase 1 gene polymorphism and lung cancer: differential susceptibility based on smoking behavior. Cancer Epidemiol Biomarkers Prev. 2001; 10:303–309. [PubMed: 11319169]
16. Schwartz AG, Yang P, Swanson GM. Familial risk of lung cancer among nonsmokers and their relatives. Am J Epidemiol. 1996; 144:554–562. [PubMed: 8797515]
17. Wenzlaff AS, Cote ML, Bock CH, Land SJ, Schwartz AG. GSTM1, GSTT1 and GSTP1 polymorphisms, environmental tobacco smoke exposure and risk of lung cancer among never smokers: a population-based study. Carcinogenesis. 2005; 26:395–401. [PubMed: 15528218]
18. Cui Y, Morgenstern H, Greenland S, Tashkin DP, Mao J, Cao W, et al. Polymorphism of Xeroderma Pigmentosum group G and the risk of lung cancer and squamous cell carcinomas of the oropharynx, larynx and esophagus. Int J Cancer. 2006; 118:714–720. [PubMed: 16094634]
19. Schwartz AG, Wenzlaff AS, Prysak GM, Murphy V, Cote ML, Brooks SC, et al. Reproductive factors, hormone use, estrogen receptor expression and risk of non small-cell lung cancer in women. J Clin Oncol. 2007; 25:5785–5792. [PubMed: 18089876]
20. Le Marchand L, Murphy SP, Hankin JH, Wilkens LR, Kolonel LN. Intake of flavonoids and lung cancer. J Natl Cancer Inst. 2000; 92(2):154–160. [PubMed: 10639518]
21. Ugolini D, Neri M, Canessa PA, Casilli C, Catrambone G, Ivaldi GP, et al. The CREST biorepository: a tool for molecular epidemiology and translational studies on malignant mesothelioma, lung cancer, and other respiratory tract diseases. Cancer Epidemiol Biomarkers Prev. 2008; 17:3013–3019. [PubMed: 18990743]
22. Sullivan SG, Greenland S. Bayesian regression in SAS software. Int J Epidemiol. 2013; 42:308–317. [PubMed: 23230299]
23. Cole SR, Chu H, Greenland S. Maximum likelihood, profile likelihood, and penalized likelihood: a primer. Am J Epidemiol. 2014; 179:252–260. [PubMed: 24173548]
24. Kim CH, Lee YC, Hung RJ, McNallan SR, Cote ML, Lim WY, et al. Exposure to secondhand tobacco smoke and lung cancer by histological type: a pooled analysis of the International Lung Cancer Consortium (ILCCO). Int J Cancer. 2014; 135:1918–1930. [PubMed: 24615328]
25. Hackshaw AK, Law MR, Wald NJ. The accumulated evidence on lung cancer and environmental tobacco smoke. BMJ. 1997; 315:980–988. [PubMed: 9365295]
26. Boffetta P. Involuntary smoking and lung cancer. Scand J Work Environ Health. 2002; 28(suppl 2):30–40. [PubMed: 12058801]

Table 1

Characteristics of adenocarcinoma in situ/minimally invasive lung adenocarcinoma cases and controls by tobacco smoking status

	All		Never smokers	
	Cases, n(%)	**Controls, n(%)**	**Cases, n(%)**	**Controls, n(%)**
Total	625	7403	170	3,035
Study				
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)

Table 2

Study-specific associations between secondhand tobacco smoke exposure and lung adenocarcinoma in situ/minimally invasive adenocarcinoma by tobacco smoking status

	All			Never smokers		
Ever exposed to secondhand smoke	**Cases, n**	**Controls, n**	**OR[1] (95% PLL)**	**Cases, n**	**Controls, n**	**OR[2] (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[3]						
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[4]						
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[5]						
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[6]						
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 for heterogeneity across studies			*0.010*			*0.005*

[1] Odds ratios are adjusted for age, sex, race/ethnicity, tobacco smoking status (ever/never), and pack-years of smoking. PLL: profile-likelihood limits

[2] Odds ratios are adjusted for age, sex, and race/ethnicity.

[3]FHS: Family Health Study.

[4]UCLA: University of California at Los Angeles

[5]WELD: Women's Epidemiology of Lung Disease

[6]CREST: Cancer of the Respiratory Tract Biorepository.

Table 3

Associations between exposure to secondhand tobacco smoke and lung adenocarcinoma in situ/minimally invasive adenocarcinoma by tobacco smoking status

	All			Never smokers		
Ever exposed to secondhand smoke	**Cases, n**	**Controls, n**	**OR[1] (95% CI)**	**Cases, n**	**Controls, n**	**OR[2] (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)

[1] Odds ratios 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.

[2] Odds ratios are adjusted for age (except for age-specific estimates), sex (except for the sex-specific estimates), and race/ethnicity.

CI: confidence intervals