IJC
International Journal of Cancer

Exposure to secondhand tobacco smoke and lung cancer by histological type: A pooled analysis of the International Lung Cancer Consortium (ILCCO)

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Key words: lung cancer, secondhand smoke, environmental tobacco smoke, involuntary smoking, International Lung Cancer Consortium
Abbreviations: CI: confidence interval; IARC: International Agency for Research on Cancer; ILCCO: International Lung Cancer Consortium; NCI: National Cancer Institute; OR: odds ratio; ROR: ratio of odds ratios; RR: risk ratio
*C.H.K., Y.C.L., and R.J.H. contributed equally to this work.
Grant sponsor: National Institutes of Health; Grant numbers: 1U19CA148127-01, R01CA060691, R01CA87895, N01PC35145, P30CA22453, CA125203, CA11386, ES011667, CA90833, CA09142, CA092824, CA74386, CA090578, CA77118, CA80127, CA115857, CA084354, P20RR018787, and R01CA 55874; Grant sponsor: German Research Foundation; Grant number: GRK1034; Grant sponsor: The Canadian Cancer Society; Grant number: CCSRI 020214; Grant sponsor: Cancer Care Ontario Research Chair Award; Grant sponsor: Karmanos Cancer Institute; Grant numbers: WSU/KCI-1 and WSU/KCI-2; Grant sponsor: Alper Research Funds for Environmental Genomics; Grant sponsor: The Mayo Foundation Fund; Grant sponsor: The Roy Castle Lung Cancer Foundation, United Kingdom; Grant Sponsor: The World Cancer Research Fund; Grant sponsor: The European Commission's INCO-COPERNICUS Program Grant number: IC15-CT96-0313; Grant sponsor: The Polish State Committee for Scientific Research; Grant number: SPUB-M-COPERNICUS/P-05/DZ-30/99/2000; Grant sponsor: The European Regional Development Fund; Grant sponsor: The State Budget of the Czech Republic, RECAMO and MH CZ DRO; Grant numbers: CZ.1.05/2.1.00/03.0101 and MMCI, 00209805; Grant sponsor: The Ministry of Health, Labor, and Welfare for the 3rd-term Comprehensive 10-year Strategy for Cancer Control of Japan; Grant sponsor: The National Cancer Center Research and Development Fund of Japan; Grant sponsor: The Ministry of Education, Science, Sports, Culture and Technology of Japan; Grant sponsor: The University of Genoa; Grant sponsor: AIRC (Associazione Italiana per la Ricerca sul Cancro); Grant sponsor: The National Medical Research Council, Singapore; Grant numbers: NMRC/1996/0155, NMRC/0897/2004, and NMRC/1075/2006
DOI: 10.1002/ijc.28835
History: Received 10 Oct 2013; Accepted 30 Jan 2014; Online 11 Mar 2014
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While the association between exposure to secondhand smoke and lung cancer risk is well established, few studies with sufficient power have examined the association by histological type. In this study, we evaluated the secondhand smoke-lung cancer relationship by histological type based on pooled data from 18 case–control studies in the International Lung Cancer Consortium (ILCCO), including 2,504 cases and 7,276 control who were never smokers and 10,184 cases and 7,176 controls who were ever smokers. We used multivariable logistic regression, adjusting for age, sex, race/ethnicity, smoking status, pack-years of smoking, and study. Among never smokers, the odds ratios (OR) comparing those ever exposed to secondhand smoke with those never exposed were 1.31 (95% CI: 1.17–1.45) for all histological types combined, 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 lung cancer, and 3.09 (95% CI: 1.62–5.89) for small cell lung cancer. The estimated association with secondhand smoke exposure was greater for small cell lung cancer than for nonsmall cell lung cancers (OR=2.11, 95% CI: 1.11–4.04). This analysis is the largest to date investigating the relation between exposure to secondhand smoke and lung cancer. Our study provides more precise estimates of the impact of secondhand smoke on the major histological types of lung cancer, indicates the association with secondhand smoke is stronger for small cell lung cancer than for the other histological types, and suggests the importance of intervention against exposure to secondhand smoke in lung cancer prevention.

What's new?

Lung cancer is the most common cause of cancer death worldwide, and it's often caused by smoking tobacco. Even if you only count people who have never smoked, lung cancer would still rank seventh, in part because of exposure to environmental tobacco smoke. This study sought to tease out how secondhand smoke affected risk of each different lung cancer type. By pooling data from 18 case-control studies, the authors determined that exposure to secondhand smoke increased the risk of small-cell lung cancer more than any other type.

Epidemiology

Lung cancer, with 1.59 million deaths in 2012, is the most common cause of cancer death worldwide.[1] Active tobacco smoking has been established as a strong risk factor for lung cancer, with an average risk ratio (RR) of 15–30.[2] Smoking is associated with increased risks of all major histological types of lung cancer, although it has been reported to be more strongly associated with small cell lung cancer (odds ratio [OR] = 12.9, 95% confidence interval [CI]: 9.79–17.1) and squamous cell carcinoma (OR = 11.3, 95% CI: 9.39–13.5) than with large cell lung cancer (OR = 5.64, 95% CI: 4.15–7.67) and adenocarcinoma (OR = 3.22, 95% CI: 2.62–3.98).[3] However, about 25% of the world's lung cancer cases are not attributable to active tobacco use.[4] Even if lung cancer cases among never smokers are considered separately from those among ever smokers, lung cancer among never smokers ranks as the seventh most common cause of cancer death worldwide.[4]

The development of lung cancer in never smokers has stimulated myriad investigations on potential risk factors for

lung cancer among those populations. Based on its review of numerous studies, the International Agency for Research on Cancer (IARC) concluded that involuntary smoking is carcinogenic to humans, with an increased risk of 20% for women and of 30% for men among never smokers who are exposed to secondhand smoke (*i.e.*, environmental tobacco smoke) from their spouse.[5] Based on an analysis of 37 epidemiological studies, Hackshaw *et al.* reported never smokers who lived with a smoker were at a 26% increased risk of lung cancer when compared with those who did not live with a smoker (95% CI: 6–47%).[6] Dose–response relationships were observed between lung cancer risk and both the number of cigarettes smoked by the spouse and the duration of exposure. The pooled relative risk was higher for squamous and small cell carcinoma (RR = 1.58, 95% CI: 1.14–2.19) than for adenocarcinoma (RR = 1.25, 95% CI: 1.07–1.46). Similarly, a pooled analysis of two case–control studies reported that duration of exposure showed consistent dose–response relationships with adenocarcinoma and squamous and small cell carcinomas and suggested a higher risk for squamous and small cell carcinomas than for adenocarcinoma.[7] However, this previous analysis was limited by inadequate power for further analysis by each histological type of lung cancer. In most of the studies to date, the number of small cell lung cancer cases among never smokers has been too small to be studied in detail.[8–10]

In this study, we aim to investigate the relationship between exposure to secondhand smoke and risk of lung cancer by histological type (adenocarcinoma, squamous cell carcinoma, large cell lung cancer, and small cell lung cancer) among ever smokers and never smokers combined and among never smokers only, using the pooled database of the International Lung Cancer Consortium (ILCCO).

Material and Methods

Study population

ILCCO was established in 2004 with the objective of sharing comparable data from ongoing lung cancer studies to increase the power for subgroup analysis. The consortium was established with funding from the National Cancer Institute (NCI) and the IARC. Investigators with eligible epidemiologic studies of lung cancer were invited to participate in the ILCCO data pooling project. A total of 56 lung cancer studies have each provided a study protocol for subject recruitment and a structured questionnaire for lifestyle information to participate in ILCCO. Details of the studies have been reported previously.[11–20]

Eighteen case–control studies in ILCCO provided the data for this analysis, all measured through structured questionnaires (Table 1). Eight studies were conducted in North America; four studies were conducted in Europe; and six studies were conducted in Asia/Oceania. Eight studies recruited healthy controls from the general population; eight studies recruited controls from hospital patients or their family or friends who did not have any smoking-related illnesses; and two studies recruited controls from mixed sources. Fifteen studies matched cases with controls on potential confounders, such as age, sex, and ethnicity, while three studies did not use matching. Written informed consents were obtained from all study participants, and each study was approved by its respective local human subject review board.

The most commonly used definition of never smokers was those who smoked less than 100 cigarettes in their lifetime (the FHS, UCLA, WELD, NELCS, SLRI, Harvard, Mayo, and IARC studies). Other definitions included those who smoked less than 180 cigarettes in their lifetime (the Hawaii study), those who smoked less than 200 cigarettes in their lifetime (the Seoul study), those who smoked less than 365 cigarettes in their lifetime (the Kyushu, Moffitt, and GEL-S studies), those who never smoked more than ten cigarettes per week regularly (the Liverpool study), or those who either smoked less than 400 cigarettes in their lifetime or less than one cigarette per day for 1 year (the CREST study). The Aichi and GenAir studies defined never smokers as those who reported they had never smoked.

We checked the data for inadmissible values, aberrant distributions, inconsistencies, and missing values and sent queries to the participating investigators to resolve all issues. We excluded from the analysis participants with unknown age (n = 31) or race/ethnicity (n = 251). We also excluded 10,442 participants with unknown secondhand smoke exposure status, of whom 7,541 were from the IARC, Moffit, or GenAir study. The IARC and Moffitt studies collected information regarding secondhand smoke exposure from never smokers only, and the GenAir study collected information regarding secondhand smoke exposure from those who either never smoked or who had stopped smoking for at least 10 years. The cases and controls excluded due to unknown exposure status had similar distributions of age, sex, and race/ethnicity as those included in the analysis.

The data for this study included 12,688 lung cancer cases and 14,452 controls, of whom 2,504 cases and 7,276 controls were never smokers and 10,184 cases and 7,176 controls were current or former smokers. Cases included patients with invasive tumors of the lung using either the International Classification of Diseases for Oncology (ICD-O) version 2 or the International Classification of Diseases (ICD), Ninth or Tenth Edition.

Statistical analysis

We performed unconditional logistic regression to obtain odds ratios (OR) with 95% confidence intervals (CI) to assess the association between exposure to secondhand smoke and lung cancer risk. All models included age (continuous), sex, race/ethnicity (White/Caucasian, Latino, Black/African-American, Asian, Native American, or other), and study center. We examined the joint effects of active smoking and exposure to secondhand smoke and tested for multiplicative interaction. We assessed various aspects of secondhand smoke exposure, including location, duration,

Table 1. Summary of studies pooled

Project/institute by region	Study name	Principal investigator	Control source	Study period	Study location
North America					
Family Health Study	FHS	A.G. Schwartz	Population	1984–1987, 1990–2003	Detroit, MI, USA
University of California at Los Angeles	UCLA	Z.F. Zhang	Population	1999–2004	Los Angeles, CA, USA
Women's Epidemiology of Lung Disease	WELD	A.G. Schwartz	Population	2001–2005	Detroit, MI, USA
New England Lung Cancer Study	NELCS	E. Duell	Population	2005–2008	New Hampshire and Vermont, USA
Samuel Lunenfeld Research Institute	SLRI	J. McLaughlin	Mixed	1997–2002	Toronto, Canada
Harvard	Harvard	D. Christiani	Hospital	1992–2008	Boston, MA, USA
Mayo Clinic	Mayo	P. Yang	Hospital	1997–2006	USA
Moffitt	Moffitt	P. Lazarus	Hospital	1999–2003	Florida, USA
Europe					
European Prospective Investigation into Cancer and Nutrition	GenAir	P. Vineis	Population	1993–1998	10 European countries
Cancer of the Respiratory Tract Biorepository	CREST	M. Neri	Mixed	1996–present	Northern Italy
Liverpool Lung Project	Liverpool	J. Field	Population	1998–2016	Liverpool, UK
International Agency for Research on Cancer	IARC	P. Boffetta	Hospital	1998–2002	Central/Eastern Europe
Asia and Oceania					
University of Hawaii	Hawaii	L. Le Marchand	Population	1992–1997	Hawaii, USA
Kyushu University	Kyushu	C. Kiyohara	Population	1994–1996	Japan
Genes and Environment in Lung Cancer, Singapore	GEL-S 1	A. Seow	Hospital	1996–1998	Singapore
Genes and Environment in Lung Cancer, Singapore	GEL-S 2	A. Seow	Hospital	2005–2007	Singapore
Aichi Cancer Center	Aichi	K. Tajima/K. Mastuo	Hospital	2001–2005	Aichi, Japan
Seoul University	Seoul	Y.C. Hong	Hospital	2001–2008	Seoul, Korea

and childhood exposure. Exposure duration variables included duration of exposure at home, duration of exposure at the workplace, and duration of exposure at home and work combined. The combined duration of exposure variable was created by summing the values for duration of exposure at home and duration of exposure at work—thus, it is the maximum possible duration of exposure, since there could be overlap between exposure periods. We performed the analyses among the total sample and among never smokers separately. For analyses among the total sample, we further adjusted the models for cigarette smoking status (ever smoker or never smoker) and pack-years of cigarette smoking (continuous) to separate the qualitative difference between ever smokers and never smokers from the quantitative impact of smoking.[21] The subanalysis of never smokers allowed us to completely eliminate the confounding effect of active smoking, assuming there was no misclassification of ever/never smoking status.

We tested for heterogeneity across the study odds ratios by using the likelihood ratio test, in which we examined the difference between the log likelihood of a model with the product term between study and the variable of interest, and

that of a model without such a product term. When there was evidence of heterogeneity in the study-specific odds ratios, we assessed the source of heterogeneity by stratified analyses. If the heterogeneity was not due to any study characteristic, we examined forest plots and performed influence analysis to assess the source of heterogeneity from any single study. For influence analysis, each study was excluded one at a time to assure that the magnitude of the overall summary estimate and p value were not dependent on any one study.

We also conducted separate analyses by lung cancer histology to compare the estimated associations of secondhand smoke with different histological subtypes. We combined bronchioloalveolar carcinomas with the rest of the adenocarcinomas; excluding them had negligible effect on the results. When comparing small cell lung cancer with nonsmall cell lung cancers, we employed a case–case approach.[22,23] All statistical analyses were performed with SAS v9.3. All p values are two-sided.

Results

The distributions of basic characteristics of the lung cancer patients and controls among the overall population and among the subsample of never smokers are shown in Table 2. The contribution of cases from the individual studies ranged from 1 to 33% and that of controls ranged from 1 to 16%. The majority of the cases and controls lived in North America. In both the overall population and the never smoker population, the proportion of older participants (65 years or above) was higher among the cases than among the controls. The proportion of men was higher in cases than in controls among the overall population, but lower among the never smoker population. The proportion of adenocarcinoma was higher among never smokers than among the overall population; the proportions of squamous cell carcinoma and small cell carcinoma were lower among never smokers than among the overall population; the proportions of large cell lung cancer were similar between the two populations.

Table 3 shows the joint effects of active smoking and exposure to secondhand smoke. Exposure to secondhand smoke was associated with an increased risk of lung cancer among both ever smokers and never smokers, and multiplicative interaction was observed between active smoking and exposure to secondhand smoke (ratio of odds ratios [ROR] = 1.33, 95% CI: 1.15–1.54).

Table 4 reports the associations between exposure to secondhand smoke and lung cancer by histological subtype in the overall study population. Compared with those never exposed to secondhand smoke, those ever exposed were at a higher risk of lung cancer (OR = 1.34, 95% CI: 1.24–1.45). Positive associations were also observed when the different histological types of lung cancer were considered separately (OR = 1.35, 95% CI: 1.23–1.48 for adenocarcinoma; OR = 1.36, 95% CI: 1.17–1.58 for squamous cell carcinoma; OR = 1.36, 95% CI: 1.04–1.79 for large cell lung cancer; and OR = 1.63, 95% CI: 1.31–2.04 for small cell lung cancer). Associations seemed to differ by exposure location. No association was observed for those exposed at work (OR = 1.02, 95% CI: 0.93–1.13), but positive associations were observed for those exposed at home (OR = 1.19, 95% CI: 1.08–1.31) and those exposed both at home and at work (OR = 1.39, 95% CI: 1.27–1.52). However, there was heterogeneity across the studies ($p < 0.001$). Risk of lung cancer increased with increasing years of exposure at home ($p < 0.001$), at work ($p = 0.02$), and at home and work combined ($p = 0.002$). Positive associations were also detected for exposure during childhood when all histological types were combined (OR = 1.15, 95% CI: 1.05–1.25) and when small cell lung cancer was examined separately (OR = 1.35, 95% CI: 1.09–1.67). The positive association between exposure during childhood and lung cancer development persisted when all types of nonsmall cell lung cancer were combined (OR = 1.12, 95% CI: 1.02–1.23; results not shown).

Stratified analyses showed that the associations between exposure to secondhand smoke and lung cancer development did not differ significantly by sex (OR = 1.23, 95% CI: 1.10–1.38 for males; OR = 1.37, 95% CI: 1.23–1.52 for females; results not shown) or race/ethnicity (OR = 1.43, 95% CI: 1.30–1.58 for Whites; OR = 1.16, 95% CI: 1.00–1.34 for Asians; OR = 0.99, 95% CI: 0.60–1.64 for Blacks; OR = 0.75, 95% CI: 0.43–1.32 for Hispanic/Latinos; results not shown). When we stratified the overall population by age (<65 years old and ≥65 years old), positive associations were observed in both age groups (OR = 1.22, 95% CI: 1.09–1.36 for <65 years old; OR = 1.45, 95% CI: 1.30–1.63 for ≥65 years old; results not shown).

Table 5 presents the associations between exposure to secondhand smoke and lung cancer by histological type among never smokers only. Exposure to secondhand smoke was associated with an increased risk of lung cancer in this population as well (OR = 1.31, 95% CI: 1.17–1.47). Positive associations were observed for all of the histological types examined, with the strongest association observed for small cell lung cancer (OR = 1.26, 95% CI: 1.10–1.44 for adenocarcinoma; OR = 1.41, 95% CI: 0.99–1.99 for squamous cell carcinoma; OR = 1.48, 95% CI: 0.89–2.45 for large cell lung cancer; OR = 3.09, 95% CI: 1.62–5.89 for small cell lung cancer). Exposure at home seemed to have a greater influence than exposure at work—the adjusted odds ratios were 1.21 (95% CI: 1.05–1.39) for those exposed at home, 1.10 (95% CI: 0.94–1.28) for those exposed at work, and 1.30 (95% CI: 1.12–1.50) for those exposed both at home and at work. Lung cancer risk tended to increase with increasing years of exposure ($p = 0.07$ for exposure at home; $p = 0.08$ for exposure at work; $p = 0.04$ for exposure at home and work combined). We did not observe an apparent association between lung cancer risk and childhood exposure to secondhand smoke (OR = 1.08, 95% CI: 0.92–1.26).

Associations between exposure to secondhand smoke and lung cancer development among never smokers were similar in males versus females (OR = 1.35, 95% CI: 1.07–1.71 for males; OR = 1.27, 95% CI: 1.11–1.45 for females; results not shown). There was some indication of heterogeneity of

Table 2. Distribution of characteristics of the overall population and never smokers

	All			Never smokers		
	Cases, *n* (%)	Controls, *n* (%)	*p* value[1]	Cases, *n* (%)	Controls, *n* (%)	*p* value[1]
Total	12,688	14,452		2,504	7,276	
study						
FHS	979(7.72)	1,173(8.12)	<0.0001	377(15.06)	678(9.32)	<0.0001
UCLA	609(4.80)	1,038(7.18)		109(4.35)	470(6.46)	
WELD	571(4.50)	571(3.95)		52(2.08)	279(3.83)	
NELCS	276(2.18)	251(1.74)		11(0.44)	95(1.31)	
SLRI	439(3.46)	928(6.42)		152(6.07)	455(6.25)	
Harvard	2,119(16.70)	1,517(10.50)		135(5.39)	479(6.58)	
Mayo	4,192(33.04)	2,235(15.46)		635(25.36)	812(11.16)	
Moffitt	117(0.92)	384(2.66)		39(1.56)	303(4.16)	
GenAir	74(0.58)	702(4.86)		47(1.88)	466(6.40)	
CREST	401(3.16)	551(3.81)		45(1.80)	237(3.26)	
Liverpool	286(2.25)	888(6.14)		17(0.68)	247(3.39)	
IARC	255(2.01)	1,012(7.00)		198(7.91)	831(11.42)	
Hawaii	628(4.95)	587(4.06)		45(1.80)	224(3.08)	
Kyushu	190(1.50)	108(0.75)		59(2.36)	57(0.78)	
GEL-S 1	261(2.06)	674(4.66)		149(5.95)	585(8.04)	
GEL-S 2	367(2.89)	748(5.18)		228(9.11)	642(8.82)	
Aichi	453(3.57)	815(5.64)		117(4.67)	319(4.38)	
Seoul	471(3.71)	270(1.87)		89(3.55)	97(1.33)	
Region						
North America	9,930(78.26)	8,684(60.09)	<0.0001	1,555(62.10)	3,795(52.16)	<0.0001
Europe	1,016(8.01)	3,153(21.81)		307(12.26)	1,781(24.48)	
Asia/Oceania	1,742(13.73)	2,615(18.09)		642(25.64)	1,700(23.36)	
Age (*years*)						
<45	1,021(8.05)	2,117(14.65)	<0.0001	285(11.38)	1,154(15.86)	<0.0001
45–49	898(7.08)	1,230(8.51)		209(8.35)	674(9.26)	
50–54	1,096(8.64)	1,608(11.13)		255(10.18)	842(11.57)	
55–59	1,609(12.68)	2,002(13.85)		300(11.98)	995(13.68)	
60–64	1,763(13.90)	1,949(13.49)		306(12.22)	900(12.37)	
65–69	2,181(17.19)	2,035(14.08)		387(15.46)	1,003(13.79)	
≥70	4,120(32.47)	3,511(24.29)		762(30.43)	1,708(23.47)	
Sex						
Men	6,378(50.27)	6,587(45.58)	<0.0001	597(23.84)	2,308(31.72)	<0.0001
Women	6,310(49.73)	7,865(54.42)		1,907(76.16)	4,968(68.28)	
Ethnicity						
Non-Hispanic White	9,478(74.70)	10,168(70.36)	<0.0001	1,543(61.62)	4,696(64.54)	<0.0001
Asian	2,131(16.80)	3,066(21.22)		766(30.59)	1,954(26.86)	
Black/African-American	540(4.26)	627(4.34)		100(3.99)	330(4.54)	
Hispanic/Latino	114(0.90)	261(1.81)		44(1.76)	132(1.81)	
Native American	218(1.72)	47(0.33)		25(1.00)	16(0.22)	
Other	207(1.63)	283(1.96)		26(1.04)	148(2.03)	

Table 2. Distribution of characteristics of the overall population and never smokers (Continued)

	All			Never smokers		
	Cases, *n* (%)	Controls, *n* (%)	*p* value[1]	Cases, *n* (%)	Controls, *n* (%)	*p* value[1]
Histology						
Adenocarcinoma	6,006(47.34)			1,555(62.10)		
Squamous cell carcinoma	2,599(20.48)			211(8.43)		
Large cell	653(5.15)			95(3.79)		
Other nonsmall cell	790(6.23)			91(3.63)		
Small cell	1,177(9.28)			79(3.15)		
Other/mixed/missing	1,463(11.53)			473(18.89)		

[1]*p* values are for χ^2 tests comparing cases and controls.

Table 3. Joint effects of active smoking and exposure to secondhand smoke on lung cancer risk

Active smoking	Exposed to secondhand smoke	Cases	Controls	Unadjusted OR (95% CI)	Adjusted OR[1] (95% CI)
Never	Never	651	2,167	1.00 Reference	1.00 Reference
Never	Ever	1,817	4,890	1.24 (1.12–1.37)	1.27 (1.14–1.42)
Ever	Never	1,219	1,074	3.78 (3.35–4.26)	2.83 (2.48–3.22)
Ever	Ever	8,827	5,921	4.96 (4.52–5.45)	4.79 (4.32–5.32)
Adjusted ratio of odds ratios[1] (95% CI)					
Overall: 1.33 (1.15–1.54)					
Adenocarcinoma: 1.44 (1.20–1.72)					
Squamous cell carcinoma: 1.12 (0.78–1.59)					
Large cell lung cancer: 1.13 (0.64–2.01)					
Small cell lung cancer: 0.79 (0.42–1.50)					

[1]Odds ratios adjusted for age, sex, race/ethnicity, and study.

associations by race/ethnicity, but the sample sizes were not large enough to obtain precise estimates for non-White populations (OR = 1.36, 95% CI: 1.18–1.58 for Whites; OR = 1.20, 0.98–1.45 for Asians; OR = 0.52, 0.25–1.06 for Blacks; OR = 1.57, 0.70–3.52 for Hispanic/Latinos; results not shown). A stronger association was observed within the older age group of never smokers than within the younger age group (OR = 1.56, 95% CI: 1.31–1.86 for ≥65 years old; OR = 1.10, 95% CI: 0.95–1.29 for <65 years old; results not shown).

Table 6 compares small cell lung cancer with nonsmall cell lung cancer in terms of their association with secondhand smoke exposure. The adjusted odds ratios comparing small cell lung cancer with nonsmall cell lung cancer were 1.28 (95% CI: 1.03–1.59) and 2.11 (95% CI: 1.11–4.04) in the overall population and among never smokers, respectively.

Discussion

This pooled analysis is the largest collaborative effort investigating the association between exposure to secondhand smoke and the development of lung cancer by histological type. Exposure to secondhand smoke was associated with an increased risk of lung cancer among both ever smokers and never smokers. Among the overall population, exposure to secondhand smoke increased the risk of lung cancer by approximately 30 and 60% for nonsmall cell lung cancer and small cell lung cancer, respectively. Among never smokers, secondhand smoke exposure increased the risk by approximately 30 and 200% for nonsmall cell lung cancer and small cell lung cancer, respectively.

Results of our joint effects analyses suggest that exposure to secondhand smoke is associated with lung cancer risk in both ever smokers as well as never smokers. The strong association between secondhand smoke exposure and lung cancer risk among ever smokers might be related to the fact that smokers exposed to secondhand smoke tend to smoke more than unexposed smokers do, as was the case in the present analysis—the mean pack-years of smoking was 42.3 among those exposed to secondhand smoke, compared with 34.5 among those who were unexposed (*t* test $p < 0.0001$; results not shown). However, the association was very strong even after adjusting for pack-years of smoking (OR = 1.40, 95% CI: 1.25–1.56; results not shown). Therefore, a potential alternative explanation for this finding is that mainstream smoke and sidestream smoke have a synergistic effect on lung cancer development.

Our results also indicate that the association with secondhand smoke exposure may be greater for small cell lung cancer than for the other histological types ($p = 0.02$). This observation is consistent with the point estimates reported in previous studies by Hackshaw *et al.* and Brennan *et al.* which

Table 4. Associations between exposure to secondhand smoke and lung cancer risk in the overall population by histological type

		All		Adenocarcinoma		Squamous cell carcinoma		Large cell lung cancer		Small cell lung cancer	
	Controls	Cases	OR[1](95% CI)	Cases	OR[1](95% CI)	Cases	OR[1](95% CI)	Cases	OR[1](95% CI)	Cases	OR[1](95% CI)
Ever exposed to secondhand smoke (based on all studies)											
Never	3,241	1,870	1.00	904	1.00	425	1.00	75	1.00	148	1.00
Ever	10,811	10,644	1.34 (1.24–1.45)	5,039	1.35 (1.23–1.48)	2,150	1.36 (1.17–1.58)	565	1.36 (1.04–1.79)	1,008	1.63 (1.31–2.04)
p for heterogeneity			0.01		0.26		0.06		0.68		0.98
Exposure location (based on all studies)											
Never exposed	3,241	1,870	1.00	904	1.00	425	1.00	75	1.00	148	1.00
Home	2,981	2,217	1.19(1.08–1.31)	1,125	1.20(1.07–1.35)	390	1.17(0.97–1.41)	127	1.27(0.93–1.74)	184	1.38(1.06–1.80)
Work	2,868	1,960	1.02(0.93–1.13)	860	1.00(0.89–1.13)	405	0.96(0.79–1.15)	102	0.97(0.69–1.38)	185	1.15(0.87–1.52)
Home and work	4,697	5,213	1.39(1.27–1.52)	2,449	1.39(1.25–1.55)	1,111	1.52(1.29–1.79)	310	1.60(1.18–2.16)	514	1.67(1.31–2.12)
p for heterogeneity			<0.001		<0.001		<0.001		0.16		0.06
Years of exposure at home (based on the FHS, UCLA, NELCS, SLRI, Moffitt, GenAir, CREST, Liverpool, IARC, and Hawaii studies)											
Never	661	374	1.00	161	1.00	94	1.00	14	1.00	9	1.00
1–20 years	2,077	1,217	1.10(0.89–1.36)	498	1.02(0.77–1.35)	245	0.95(0.65–1.40)	111	1.23(0.59–2.59)	132	1.45(0.65–3.24)
>20 years	1,350	1,163	1.36(1.11–1.65)	461	1.31(1.01–1.69)	246	1.14(0.81–1.62)	66	1.90(0.96–3.77)	124	2.28(1.04–4.98)
p for heterogeneity			0.18		0.88		0.83		0.35		0.71
p for trend			<0.001		0.004		0.19		0.01		0.001
Years of exposure at work (based on the FHS, UCLA, NELCS, SLRI, Moffitt, GenAir, CREST, Liverpool, IARC, and Hawaii studies)											
Never	1,204	570	1.00	243	1.00	103	1.00	31	1.00	28	1.00
1–20 years	2,239	1,205	1.03(0.88–1.21)	504	1.03(0.83–1.28)	187	0.97(0.70–1.34)	120	1.19(0.71–1.99)	133	1.04(0.62–1.72)
>20 years	1,511	1,192	1.19(1.02–1.40)	441	1.21(0.98–1.49)	299	1.25(0.93–1.68)	52	0.99(0.58–1.66)	131	1.39(0.84–2.30)
p for heterogeneity			0.02		0.17		0.14		0.71		0.31
p for trend			0.02		0.05		0.05		0.79		0.08
Combined years of exposure at home and work (based on the FHS, UCLA, NELCS, SLRI, Moffitt, GenAir, CREST, Liverpool, IARC, and Hawaii studies)											
Never	517	231	1.00	121	1.00	47	1.00	10	1.00	6	1.00
1–20 years	1,020	488	0.93(0.73–1.19)	262	0.87(0.65–1.17)	51	0.66(0.40–1.10)	33	0.53(0.22–1.25)	26	1.27(0.46–3.52)
21–40 years	1,024	759	1.12(0.89–1.42)	351	0.99(0.74–1.32)	128	1.13(0.72–1.76)	53	0.75(0.33–1.70)	68	1.97(0.76–5.13)
>40 years	973	971	1.26(0.99–1.60)	406	1.12(0.84–1.51)	203	1.26(0.81–1.96)	40	1.03(0.44–2.38)	90	2.25(0.87–5.77)
p for heterogeneity			0.006		0.004		0.09		0.97		0.97
p for trend			0.002		0.09		0.01		0.13		0.01

Table 4. Associations between exposure to secondhand smoke and lung cancer risk in the overall population by histological type (Continued)

	Controls	All		Adenocarcinoma		Squamous cell carcinoma		Large cell lung cancer		Small cell lung cancer	
		Cases	OR[1](95% CI)	Cases	OR[1](95% CI)	Cases	OR[1](95% CI)	Cases	OR[1](95% CI)	Cases	OR[1](95% CI)
Childhood exposure (based on the FHS, UCLA, NELCS, SLRI, Mayo, Moffitt, and GenAir studies)											
No	2,076	2,081	1.00	1,029	1.00	420	1.00	80	1.00	159	1.00
Yes	3,752	4,156	1.15(1.05–1.25)	1,814	1.10(0.99–1.22)	822	1.10(0.94–1.29)	230	1.17(0.88–1.54)	457	1.35(1.09–1.67)
p for heterogeneity			0.60		0.74		0.80		0.24		0.93

[1]Odds ratio adjusted for age, sex, race/ethnicity, study, smoking status, and pack–years of smoking.

also evaluated the association between secondhand smoke exposure and lung cancer risk, but with small and squamous cell carcinomas combined.[6,7] Detecting such clear associations has been particularly challenging for small cell lung cancer due to the small number of cases among never smokers. In our study, the difference in the magnitudes of the association among the overall population compared with never smokers may be due to chance or residual confounding.

Epidemiologic studies have consistently reported that cigarette smoking is most strongly associated with small cell lung cancer, followed by squamous cell carcinoma.[3,10,23–28] The differences in the strengths of associations by histological type is thought to be related to tumor location. Small cell lung cancer and squamous cell carcinoma mainly occur in the large central bronchi whereas adenocarcinoma and large cell lung cancer arise from more peripheral sites. The aerodynamic diameters of cigarette smoke particles determine the sites of deposition in the regions of the lung.[29] It has been hypothesized that sites that are more proximal in the respiratory tract are more heavily exposed to tobacco smoke particles, especially those of larger size, than are peripheral sites.[25,30,31] De Stefani *et al.* suggested that the presence of carcinogenic radioactive compounds and heavy metals in tobacco smoke could also explain the strong relation between exposure to tobacco smoke and small cell lung cancer, since occupational exposure to these carcinogens are strongly associated with small cell lung cancer.[23] Many of these carcinogens (*e.g.*, nickel, chromium, and arsenic) are also major constituents of sidestream smoke.[5] The results of our study suggest that cigarette smoke plays a major role in the development of small cell lung cancer not only in the form of mainstream smoke affecting active smokers but also in the form of sidestream smoke affecting both active and passive smokers.

Lung cancer histology seems to be dictated by genetic alterations and the type of cells in which they occur. In a study using precise laser capture microdissection and allelotyping, Wistuba *et al.* reported there were differences in specific genetic alterations detected in small cell lung cancer compared with nonsmall cell lung cancers, and the smoking-damaged bronchial epithelium of patients with small cell lung cancer showed considerably more genetic damage—in terms of allele loss and microsatellite alterations—than that of patients with nonsmall cell lung cancers.[32] Furthermore, many genetic alterations were also frequently observed in histologically normal and mildly abnormal bronchial biopsies from current and former smokers.[32] Rb and p53 mutations, which occur in up to 90% of human small cell lung cancers, are examples of genetic damage caused by smoking. In a study to establish a mouse model for small cell lung cancer, Meuwissen *et al.* demonstrated that concomitant loss of Rb and p53 in a broad range of mouse lung epithelial cells gave rise almost exclusively to small cell lung cancer.[33] Although the cellular origin of lung cancer is largely unknown, it is speculated that different histological types arise from distinct cells of origin located in defined microenvironments, and

Table 5. Associations between exposure to secondhand smoke and lung cancer risk among never smokers by histological type

		All		Adenocarcinoma		Squamous cell carcinoma		Large cell lung cancer		Small cell lung cancer	
	Controls	Cases	OR[1](95% CI)	Cases	OR[1](95% CI)	Cases	OR[1](95% CI)	Cases	OR[1](95% CI)	Cases	OR[1](95% CI)
Ever exposed to secondhand smoke (based on all studies)											
Never	2,167	651	1.00	422	1.00	52	1.00	22	1.00	13	1.00
Ever	4,890	1,817	1.31(1.17–1.47)	1,119	1.26(1.10–1.44)	156	1.41(0.99–1.99)	72	1.48(0.89–2.45)	65	3.09(1.62–5.89)
p for heterogeneity			0.02		0.10		0.36		0.19		0.99
Exposure location (based on all studies)											
Never exposed	2,167	651	1.00	422	1.00	52	1.00	22	1.00	13	1.00
Home	1,712	626	1.21(1.05–1.39)	405	1.20(1.02–1.42)	49	1.21(0.79–1.86)	26	1.24(0.68–2.24)	20	3.17(1.46–6.85)
Work	1,408	410	1.10(0.94–1.28)	215	1.00(0.83–1.21)	41	1.11(0.71–1.74)	17	1.45(0.74–2.86)	17	2.21(1.01–4.86)
Home and work	1,654	602	1.30(1.12–1.50)	386	1.25(1.05–1.49)	61	1.93(1.29–2.91)	23	1.57(0.83–2.98)	25	3.40(1.66–6.94)
p for heterogeneity			<0.001		<0.001		0.02		0.31		1.00
Years of exposure at home (based on the FHS, UCLA, NELCS, SLRI, Moffitt, GenAir, CREST, Liverpool, IARC, and Hawaii studies)											
Never	390	130	1.00	63	1.00	19	1.00	7	1.00	4	1.00
1–20 years	924	263	1.32(0.97–1.81)	133	1.21(0.80–1.83)	32	1.58(0.80–3.14)	15	0.84(0.25–2.76)	13	1.88(0.54–6.63)
>20 years	568	229	1.35(1.01–1.82)	128	1.34(0.92–1.96)	30	1.56(0.81–3.01)	11	1.18(0.42–3.31)	11	2.20(0.66–7.39)
p for heterogeneity			0.04		0.06		0.35		0.96		0.90
p for trend			0.07		0.13		0.22		0.66		0.22
Years of exposure at work (based on the FHS, UCLA, NELCS, SLRI, Moffitt, GenAir, CREST, Liverpool, IARC, and Hawaii studies)											
Never	757	263	1.00	132	1.00	26	1.00	12	1.00	7	1.00
1–20 years	1,059	274	1.15(0.91–1.45)	130	1.12(0.81–1.54)	29	1.54(0.81–2.93)	23	2.30(0.95–5.57)	16	1.68(0.62–4.60)
>20 years	579	185	1.26(0.97–1.63)	95	1.36(0.98–1.90)	38	1.88(1.04–3.39)	2	0.35(0.07–1.66)	12	2.13(0.74–6.10)
p for heterogeneity			0.03		0.41		0.14		0.90		0.99
p for trend			0.08		0.07		0.04		0.49		0.16
Combined years of exposure at home and work (based on the FHS, UCLA, NELCS, SLRI, Moffitt, GenAir, CREST, Liverpool, IARC, and Hawaii studies)											
Never	315	80	1.00	51	1.00	9	1.00	5	1.00	1	1.00
1–20 years	557	160	1.12(0.78–1.61)	80	0.90(0.58–1.39)	11	1.16(0.44–3.11)	8	0.71(0.20–2.58)	7	3.76(0.42–33.63)
21–40 years	445	173	1.33(0.93–1.89)	93	1.16(0.76–1.77)	21	1.80(0.75–4.31)	11	1.18(0.36–3.86)	7	3.90(0.45–33.53)
>40 years	305	132	1.40(0.96–2.04)	69	1.25(0.79–1.97)	28	2.71(1.17–6.28)	4	0.81(0.20–3.26)	6	4.85(0.57–41.40)
p for heterogeneity			0.02		0.05		0.44		0.99		1
p for trend			0.04		0.13		0.006		0.84		0.17

Table 5. Associations between exposure to secondhand smoke and lung cancer risk among never smokers by histological type (Continued)

	Controls	All		Adenocarcinoma		Squamous cell carcinoma		Large cell lung cancer		Small cell lung cancer	
		Cases	OR[1](95% CI)	Cases	OR[1](95% CI)	Cases	OR[1](95% CI)	Cases	OR[1](95% CI)	Cases	OR[1](95% CI)
Childhood exposure (based on the FHS, UCLA, NELCS, SLRI, Mayo, Moffitt, and GenAir studies)											
No	1,081	485	1.00	318	1.00	26	1.00	12	1.00	8	1.00
Yes	1,611	563	1.08(0.92–1.26)	304	0.97(0.81–1.18)	35	1.19(0.69–2.03)	20	1.49(0.70–3.15)	17	1.76(0.74–4.22)
p for heterogeneity			0.29		0.48		0.65		0.59		0.63

[1]Odds ratio adjusted for age, sex, race/ethnicity, and study.

small cell lung cancer is thought to have its origin in neuroendocrine cells.[33–35]

We also observed some variations in strengths of associations by the location and duration of secondhand smoke exposure. Exposure at home seemed to have a stronger effect than exposure at the workplace, probably because exposure at home—especially from a spouse—is more likely to be of greater duration and intensity than exposure at work. The results also suggest that people exposed to secondhand smoke both at home and at the workplace are more likely to develop lung cancer than those exposed at one location only. For both exposure at home and exposure at work, we observed dose–response relations between duration of exposure and lung cancer incidence. The trends were more evident among the overall population than among the subgroup of never smokers, possibly due to the difference in sample sizes. Brennan *et al.* also reported such dose–response relations among never smokers, but their method of categorizing duration of exposure differed from ours.[7] When we used the same duration categories used by Brennan *et al.* ($<$16/16–30.9/$\geq$31.0 years for exposure from the spouse—assumed to be comparable to our variable for exposure at home—and $<$8.0/8.0–20.9/$\geq$21.0 years for exposure at work), we observed dose–response relations among never smokers for both exposure at home ($p = 0.04$) and exposure at work ($p = 0.02$). Lastly, exposure to secondhand smoke during childhood was associated with lung cancer among the overall population. Results from previous studies of exposure to secondhand smoke during childhood have been inconsistent, which could be, at least partially, due to the difficulty of recalling exposures that took place a long time ago.[36–49] The inconsistency may also be due to chance, since some studies had low power.

This study has several limitations. Due to the nature of our case–control study design, the results might be influenced to some degree by recall bias. Since tobacco is an established risk factor for many diseases, hospital-based controls might be more likely than healthy controls to recall their exposure to secondhand smoke. If this is in fact the case, our results from hospital-based case–control studies might be more likely to be biased towards the null, compared to those from population-based studies. However, when we performed stratified analysis, the association between exposure to secondhand smoke and lung cancer development was even stronger within the stratum of hospital-based studies than that of population-based studies. Variations in the definition of never smokers across studies could also be a limitation. However, consistent results from influence analysis confirmed that the observed associations were not due to any particular study. Another potential source of bias might be the result of misclassification of ever smokers as never smokers due to misreporting. In addition, the concordance of smoking status within couples might lead to bias of the estimates. Although we were not able to assess this issue in this pooled population, a European validation study has suggested that such bias from smoker misclassification is not likely to be significant.[50] If a disproportionate number of exposed controls had been classified as unexposed, then this might bias

Table 6. Difference of associations with exposure to secondhand smoke between small cell lung cancer and nonsmall cell lung cancer

			Unadjusted				Adjusted[2]			
Histological type	**Cases**	**Controls**	**OR**	**(95% CI)**	**OR[1]**	**(95% CI)**	**OR**	**(95% CI)**	**OR[1]**	**(95% CI)**
Overall population										
Nonsmall cell lung cancer	9,941	14,052	1.72	(1.61–1.84)	1.00		1.34	(1.23–1.46)	1.00	
Small cell lung cancer	1,156	14,052	2.04	(1.71–2.44)	1.19	(0.99–1.43)	1.63	(1.31–2.04)	1.28	(1.03–1.59)
			Unadjusted				**Adjusted[3]**			
Histological type	**Cases**	**Controls**	**OR**	**(95% CI)**	**OR[1]**	**(95% CI)**	**OR**	**(95% CI)**	**OR[1]**	**(95% CI)**
Never smokers										
Nonsmall cell lung cancer	1,931	7,057	1.20	(1.07–1.35)	1.00		1.28	(1.13–1.45)	1.00	
Small cell lung cancer	78	7,057	2.22	(1.22–4.03)	1.84	(1.01–3.37)	3.09	(1.62–5.89)	2.11	(1.11–4.04)

[1]Odds ratio for developing small cell lung cancer compared with nonsmall cell lung cancer with respect to exposure to secondhand smoke, using case-case study methods.
[2]Odds ratio adjusted for age, sex, race/ethnicity, study, smoking status, and pack-years of smoking.
[3]Odds ratio adjusted for age, sex, race/ethnicity, and study.

the estimated association away from the null. Finally, we excluded some participants from the analysis due to missing data, mostly on exposure status. Selection bias is possible if the data were not missing at random. However, comparing those excluded from the analysis with those included, the distributions of the covariates were similar between the two groups, except for study site.

The strength of this study is the relatively high power achieved through the pooling of individual-level data. Compared with meta-analyses, pooled analyses such as ours can achieve high power with less publication bias and more consistent covariate adjustment. Although our results point to the role of secondhand smoke in the development of lung cancer regardless of histological type, the extent of the relationship varies by histological type and is especially strong for small cell lung cancer.

While it is important to disseminate the public health message about the hazard of active and passive smoking in order to reduce the incidence of lung cancer, further investigation on the etiologic processes underlying the association between tobacco smoke and lung cancer are warranted. Future studies should also determine if exposure to secondhand smoke is associated with stage of lung cancer, as well as consider other potential risk factors, including indoor air pollution from other sources and genetic factors. In the ILCCO consortium, we have started the process of pooling genetic data in order to investigate the role of genetic polymorphisms in the DNA repair genes in the development of lung cancer among never smokers.

Acknowledgements

This work was supported by the National Institutes of Health (1U19CA148127-01); the German Research Foundation (GRK1034); the Canadian Cancer Society (CCSRI 020214); and Cancer Care Ontario Research Chair Award. Studies of the Wayne State University were supported by the Karmanos Cancer Institute (WSU/KCI-1, WSU/KCI-2) and the National Institutes of Health (R01CA060691, NIH R01CA87895, NIH N01-PC35145, NIH P30CA22453, CA125203). The UCLA study was supported by the National Institutes of Health (CA 11386, ES011667, CA 90833, and CA 09142) and Alper Research funds for Environmental Genomics. The Harvard study was supported by the National Institutes of Health (CA092824, CA74386 and CA090578). The Mayo Clinic (MAYO) studies were supported by the Mayo Foundation Fund and the National Institutes of Health (CA77118, CA80127, CA115857, CA084354 to P.Y.]. The New England Lung Cancer Study was supported by the National Institutes of Health (P20 RR018787). The Hawaii study was supported by the National Institutes of Health (R01CA 55874). The Liverpool Lung Project (LLP) was supported by the Roy Castle Lung Cancer Foundation UK. The Central Europe study (CE) was supported by the World Cancer Research Fund and the European Commission's INCO-COPERNICUS Program (contract number IC15-CT96-0313). The Warsaw part of CE was supported by the Polish State Committee for Scientific Research (SPUB-M-COPERNICUS/P-05/DZ-30/99/2000). The Czech Republic part of CE was supported in part by the European Regional Development Fund and the State Budget of the Czech Republic, RECAMO (CZ.1.05/2.1.00/03.0101) and MH CZ - DRO (MMCI, 00209805). The Aichi study was supported in part by Grants-in-Aid from the Ministry of Health, Labor, and Welfare for the 3rd-term Comprehensive 10-year Strategy for Cancer Control; the National Cancer Center Research and Development Fund; and Grant-in-Aid for Scientific Research on Priority Areas and on Innovative Area from the Ministry of Education, Science, Sports, Culture, and Technology of Japan. The CREST study was supported by the University of Genoa and AIRC (Associazione Italiana per la Ricerca sul Cancro). The Genes and Environment in Lung Cancer, Singapore (GEL-S) study was supported by the National Medical Research Council, Singapore (NMRC/1996/0155, NMRC/0897/2004 and NMRC/1075/2006).

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