Lung Cancer Among Firefighters: Smoking-Adjusted Risk Estimates in a Pooled Analysis of Case-Control Studies

Carolina Bigert, MD, PhD, Per Gustavsson, MD, PhD, Kurt Straif, MD, PhD, Dirk Taeger, PhD, Beate Pesch, PhD, Benjamin Kendzia, MSc, Joachim Schüz, PhD, Isabelle Stücker, PhD,
Florence Guida, PharmD, Irene Brüske, MD, Heinz-Erich Wichmann, PhD, Angela C. Pesatori, MD, PhD, Maria Teresa Landi, MD, PhD, Neil Caporaso, MD, Lap Ah Tse, PhD, Ignatius Tak-sun Yu, PhD, Jack Siemiatycki, PhD, Jérôme Lavoué, PhD, Lorenzo Richiardi, MD, PhD, Dario Mirabelli, MD,
Lorenzo Simonato, MD, Karl-Heinz Jöckel, PhD, Wolfgang Ahrens, PhD, Hermann Pohlabeln, PhD, Adonina Tardón, PhD, David Zaridze, MD, PhD, John K. Field, PhD, Andrea 't Mannetje, PhD, Neil Pearce, PhD, John McLaughlin, PhD, Paul Demers, PhD, Neonila Szeszenia-Dabrowska, PhD,
Jolanta Lissowska, PhD, Peter Rudnai, MD, Eleonora Fabianova, MD, PhD, Rodica Stanescu Dumitru, PhD, Vladimir Bencko, MD, PhD, Lenka Foretova, MD, PhD, Vladimir Janout, PhD, Paolo Boffetta, MD, MPH, Susan Peters, PhD, Roel Vermeulen, PhD, Hans Kromhout, PhD, Thomas Brüning, MD, PhD, and Ann C. Olsson, PhD

Objectives: The aim of this study was to explore lung cancer risk among firefighters, with adjustment for smoking. **Methods:** We used pooled information from the SYNERGY project including 14 case-control studies conducted in Europe, Canada, New Zealand, and China, with lifetime work histories and smoking habits for 14,748 cases of lung cancer and 17,543 controls. We estimated odds ratios by unconditional logistic regression with adjustment for smoking and having ever been employed in a job known to present an excess risk of lung cancer. **Results:** There was no increased lung cancer risk overall or by specific cell type among firefighters (n = 190), neither before nor after smoking adjustment. We observed no significant exposure-response relationship in terms of work duration. **Conclusions:** We found no evidence of an excess lung cancer risk related to occupational exposure as a firefighter.

F irefighters have a potential for exposure to different types of chemical compounds by inhalation of particulate matter, gases, and vapors during the course of their work. A large number of known (eg, arsenic, asbestos, benzene, benzopyrene, 1,3-butadiene, cadmium, formaldehyde and silica) or suspected (eg, acetaldehyde, naphthalene, polychlorinated biphenyls, styrene, tetrachlorethylene,

From The Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden (Drs Bigert, Gustavsson); International Agency for Research on Cancer, Lyon, France (Drs Straif, Schüz, Olsson); Institute for Prevention and Occupational Medicine of the German Social Accident Insurance - Institute of the Ruhr-Universität Bochum (IPA), Bochum, Germany (Drs Taeger, Pesch, Kendzia, Brüning); Inserm, Centre for Research in Epidemiology and Population Health (CESP), U1018, Environmental Epidemiology of Cancer Team (Drs Stücker, Guida); Université Paris-Sud, UMRS 1018, F-94807, Villejuif, France (Drs Stücker, Guida); Institut für Epidemiologie I, Deutsches Forschungszentrum für Gesundheit und Umwelt, Neuherberg (Dr Brüske); Institute of Medical Informatics, Biometry and Epidemiology, Ludwig Maximilians University (Dr Wichmann); Helmholtz Center Munich, Institute of Epidemiology I (Dr Wichmann); Institute of Medical Statistics and Epidemiology, Technical University Munich, Munich, Germany (Dr Wichmann); Department of Clinical Sciences and Community Health, Università degli Studi di Milano and IRCCS Ca' Granda Foundation, Milan, Italy (Dr Pesatori); National Cancer Institute, Bethesda, Maryland (Drs Landi, Caporaso); Division of Occupational and Environmental Health, School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong, China (Drs Tse, Yu); Research Centre of University of Montréal Hospital Centre, University of Montréal, Montréal, Quebec, Canada (Drs Siemiatycki, Lavoué); Cancer Epidemiology Unit, Department of Medical Sciences, University of Turin, Turin, Italy (Drs Richiardi, Mirabelli); Department of Environmental Medicine and Public Health, University of Padua, Padua, Italy (Dr Simonato);

trichlorethylene, and toluene diisocyanates) human carcinogens have been detected in smoke at fires, several of which are known to cause lung cancer.¹ Many of the carcinogens identified are volatile organic compounds (VOCs) common to most burning materials and are dominated by benzene, toluene, and naphthalene.^{1,2} Firefighters may also be exposed to exhaust from diesel engines, which is known to increase the risk of lung cancer.³ The exposure may vary widely among firefighters depending on the type of work activities, time spent at fires, and use of respiratory equipment. They are exposed mainly by inhalation, but for some chemicals, such as polycyclic aromatic hydrocarbons and polychlorinated biphenyls, exposure through dermal absorbation may also be important.¹ "Occupational exposure as a firefighter" has been evaluated by the International Agency for Research on Cancer (IARC) and classified as "possibly carcinogenic to humans," with strongest evidence for testicular cancer, prostate cancer, and non-Hodgkin lymphoma.¹

Some previous studies among firefighters indicate an excess of lung cancer overall,^{4–6} lung cancer of a specific cell type,^{7.8} or positive exposure-response associations,⁹ whereas most studies do not.^{10–20} Pukkala et al⁷ observed an increased incidence of lung adenocarcinoma among firefighters in the Nordic countries, Tsai et al⁸ observed an

Institute for Medical Informatics, Biometry and Epidemiology, University of Duisburg-Essen, Essen, Germany (Dr Jöckel); Leibniz Institute for Prevention Research and Epidemiology - BIPS, Bremen, Germany (Drs Ahrens, Pohlabeln); CIBERESP, University of Oviedo, Oviedo, Spain (Dr Tardón); Russian Cancer Research Centre, Moscow, Russia (Dr Zaridze); Roy Castle Lung Cancer Research Programme, Cancer Research Centre, University of Liverpool, Liverpool, UK (Dr Field); Centre for Public Health Research, Massey University, Wellington, New Zealand (Drs 't Mannetje, Pearce); Public Health Ontario, Toronto (Dr McLaughlin); Occupational Cancer Research Centre, Cancer Care Ontario, Ontario, Toronto, Canada (Dr Demers); The Nofer Institute of Occupational Medicine, Lodz (Dr Szeszenia-Dabrowska); The M Sklodowska-Curie Cancer Center and Institute of Oncology, Warsaw, Poland (Dr Lissowska); National Public Health Center, Budapest, Hungary (Dr Rudnai); Regional Authority of Public Health, Banska Bystrica, Slovakia (Dr Fabianova); Institute of Public Health, Bucharest, Romania (Dr Stanescu Dumitru); Institute of Hygiene and Epidemiology, 1st Faculty of Medicine, Charles University, Prague (Dr Bencko); Masaryk Memorial Cancer Institute, Brno, Czech Republic (Dr Foretova); Palacky University, Faculty of Medicine, Olomouc (Dr Janout); Faculty of Medicine, Ostrava University, Ostrava, Czech Republic (Dr Janout); The Tisch Cancer Institute and Institute for Translational Epidemiology, Icahn School of Medicine at Mount Sinai, New York, New York (Dr Boffetta); Institute for Risk Assessment Sciences, Utrecht, the Netherlands (Drs Peters, Vermeulen, Kromhout); and Occupational Respiratory Epidemiology, School of Population Health, University of Western Australia, Perth, Western Australia, Australia (Dr Peters).

excess risk of nonspecific, nonsmall cell lung cancer among California firefighters, Hansen²¹ observed an increase in lung cancer mortality in the oldest age group of Danish firefighters, and in a study by Heyer et al,²² the lung cancer mortality among Seattle firefighters was elevated in the oldest age group. Further, a large comprehensive review and meta-analysis by LeMasters et al²³ evaluated cancer risk among firefighters. The lung cancer risk was classified as unlikely with a summary risk estimate of 1.03 [95% confidence interval (95% CI) 0.97 to 1.08].²³ Overall, findings from previous studies of cancer in firefighters have been inconsistent. In particular, few studies have provided evidence of increased lung cancer risk among firefighters, although inhalation is a primary route of exposure. Negative confounding by smoking is one among the possible explanations of the absence of excess of lung cancer risk in previous studies, which nearly all lack information on tobacco use. Only two of the above-mentioned lung cancer studies had adequate information on individual smoking habits.^{4,15} Previous studies have shown diverging results regarding lung cancer of various cell types among firefighters,^{4,7,8,10} and the impact of smoking on lung cancer risk may vary between different histological subtypes of lung cancer.24

The aim of this study was to explore lung cancer risk among firefighters taking into account individual lifetime history of smoking and having ever been employed in a job with established lung cancer risk. We also aimed to analyze the results by cell types.

METHODS

We used pooled information from the SYNERGY project including case-control studies conducted in Europe, Canada, New Zealand, and China, with data on lifetime work histories and individual smoking habits. The SYNERGY project has already been described in detail elsewhere.^{25,26} In a previous paper in this journal, we reported lung cancer risk among cooks using the same database and methods,²⁶ with only minor differences, mainly regarding included studies. Therefore, only part of the study setting and methods is repeated in the present article. Table 1 provides information about the studies included in the present analysis.^{27–39} The SYNERGY studies included both men and women, but only two women had ever worked as a firefighter (zero cases and two controls); therefore, the analysis was restricted to men. Three of the original studies (Rome, Paris, and MORGEN) had no firefighters among either cases or controls, and were therefore omitted. The present analysis included 14,748

This study was funded by AFA Insurance in Sweden (grant no. 130104). AFA Insurance is owned by Sweden's labor market parties: the Confederation of Swedish Enterprise, the Swedish Trade Union Confederation and The Council for Negotiation and Co-operation. The SYNERGY project is funded by the German Social Accident Insurance (DGUV). The original studies were funded by a list of agencies, including the Canadian Institutes for Health Research and Guzzo-SRC Chair in Environment and Cancer, the National Cancer Institute of Canada with funds provided by the Canadian Cancer Society and Cancer Care Ontario; the French agency of health security (ANSES), the Fondation de France, the French National Research Agency (ANR), the National Institute of Cancer (INCA), the Fondation for Medical Research (FRM), the French Institute for Public Health Surveillance (InVS), the Health Ministry (DGS), the Organization for the Research on Cancer (ARC), and the French Ministry of work, solidarity and public function (DGT). In Germany, the studies were funded by the Federal Ministry of Education, Science, Research, and Technology grant no. 01 HK 173/0 and the Federal Ministry of Science and the Ministry of Labour and Social Affairs. The INCO study was supported by a grant from the European Commission's INCO-COPERNICUS program, a grant from the Polish State Committee for Scientific Research, and the Roy Castle Foundation as part of the Liverpool Lung Project. In Brno, Czech Republic, the study was supported by MH CZ – DRO (MMCI, 00209805) in the INCO part. The EAGLE study was funded by the Intramural Research Program of the National Institutes of Health, National Cancer Institute, Division of Cancer Epidemiology and Genetics, Bethesda, MD; the Environmental Epidemiology Program of the Lombardy Region, Italy;

male lung cancer cases and 17,543 male controls, after excluding 132 cases and 149 controls with incomplete information on smoking or work history and 230 cases and 239 controls who never worked for at least 1 year.

Identification of Firefighters

We identified 190 male firefighters (86 lung cancer cases, 104 controls) from the ISCO-68 code ("5-81").⁴⁰ The group "Firefighters" includes "General firefighters" (66 cases, 89 controls), "Fire prevention firefighters" (nine cases, four controls), "Aircraft accident firefighters" (zero cases, three controls), and "Other firefighters" (15 cases, 12 controls). Some of them had worked as two types of firefighters (four cases, four controls). Therefore, the sum of the number of firefighters in the different categories differs from that of all firefighters.

Statistical Methods

Detailed information on the statistical analyses has been presented elsewhere.²⁶ In summary, we estimated odds ratios (ORs) by unconditional logistic regression with adjustment for study and age (OR1), additional adjustment for cumulative cigarette smoking and time since quitting smoking (OR2), and having ever been employed in a job known to present an excess risk of lung cancer ("List A" job) (OR3), such as occupations in the mining and quarrying industry, asbestos production, metals industry, construction industry (insulators and pipe coverers, roofers, asphalt workers, and painters), and shipbuilding.^{41,42}

The analyses were repeated in relation to smoking status (never, former, current), work duration (<6, 6 to 21, 22 to 32, >32 years), major cell types of lung cancer (adenocarcinoma, squamous cell carcinoma, small cell carcinoma, others/unspecified), and for employment as a "General firefighter" (ie, excluding "Fire prevention firefighters," "Aircraft accident firefighters," and "Other firefighters"). As the reference category, we always used all those who had never worked as firefighters.

We used meta-analysis to explore study-specific ORs for firefighters and the extent of heterogeneity across the studies. The "metan" command in Stata was used specifying a fixed effect model using the method of Mantel and Haenszel. We used the *I*-squared measure (describes the percentage of total variation between studies due to heterogeneity) to quantify heterogeneity. The I^2 was estimated to be zero, which implies that there was no more variation between study estimates than would be expected by

and the Istituto Nazionale per l'Assicurazione contro gli Infortuni sul Lavoro, Rome, Italy. The TURIN study was supported by the Italian Association for Cancer Research, Region Piedmont, Compagnia di San Paolo. The CAPUA study was supported by the Instituto Universitario de Oncologia, Universidad de Oviedo, Asturias, the Fondo de Investigacion Sanitaria (FIS), and the Ciber de Epidemiologia y Salud Publica (CIBER-ESP), Spain. The Hong Kong study was supported by a grant from the Research Grants Council of the Hong Kong Special Administrative Region, China. The OCANZ study was funded by the Health Research Council of New Zealand, the New Zealand Department of Labour, Lottery Health Research, and by the Cancer Society of New Zealand. The Swedish study LUCAS was supported by the Swedish Council for Work Life Research and the Swedish EPA.

The authors do not have any competing financial interests.

Ethical approvals for the original studies were obtained in accordance with legislation in each country, and for the SYNERGY project from the IARC Institutional Review Board Committee. The Regional Ethics Committee in Stockholm, Sweden, gave approval for the present analyses.

Lung cancer among firefighters: smoking-adjusted risk estimates in a pooled analysis of case-control studies.

Address correspondence to: Dr Carolina Bigert, MD, PhD, Institute of Environmental Medicine, Karolinska Institutet, Solnavägen 4 10th Floor, SE-113 65 Stockholm, Sweden (carolina.bigert@ki.se).

Copyright © 2016 American College of Occupational and Environmental Medicine

DOI: 10.1097/JOM.00000000000878

TABLE 1. Description of SYNERGY Studies 1985–2010 Included in Analysis, Men and Women

				(Cases	Co	ontrols			
First Author, Year (Reference No.)	Study (Short Names)	Country	Data Collection	No.	Response Rate (%)	No.	Response Rate (%)	Source of Controls	Data Source	Interviewee
Brüske-Hohlfeld et al ²⁷	AUT-MUNICH	Germany	1990-1995	3,180	77	3,249	41	Р	Ι	S
Jöckel et al ²⁸	HdA	Germany	1988-1993	1,004	69	1,004	68	Р	Ι	S
Consonni et al ²⁹	EAGLE	Italy	2002-2005	1,943	87	2,116	72	Р	Ι	S
Richiardi et al ³⁰	TURIN/VENETO	Italy	1990-1994	1,132	79	1,553	80	Р	Ι	S
Stücker et al ³¹	LUCA	France	1989-1992	309	98	302	98	Н	Ι	S
Guida et al ³²	ICARE	France	2001-2007	2,926	87	3,555	81	Р	Ι	S & NOK
López-Cima et al ³³	CAPUA	Spain	2000-2010	875	91	838	96	Н	Ι	S
Scélo et al ³⁴	INCO	Czech Republic	1999-2002	304	94	453	80	Н	Ι	S
Scélo et al 34	INCO	Hungary	1998-2001	402	90	315	100	Н	Ι	S
Scélo et al ³⁴	INCO	Poland	1998-2002	800	88	841	88	Р&Н	Ι	S
Scélo et al 34	INCO	Slovakia	1998-2002	346	90	285	84	Н	Ι	S
Scélo et al 34	INCO	Romania	1998-2002	181	90	228	99	Н	Ι	S
Scélo et al 34	INCO	Russia	1998-2001	600	96	580	90	Н	Ι	S
Scélo et al 34	INCO-LLP	United Kingdom	1998-2005	442	78	918	84	Р	Ι	S
Gustavsson et al ³⁵	LUCAS	Sweden	1985-1990	1,042	87	2,356	85	Р	Q	S & NOK
Corbin et al ³⁶	OCANZ	New Zealand	2003-2009	457	53	792	48	Р	I & T	S & NOK
Ramanakumar et al ³⁷	MONTREAL	Canada	1996-2002	1,203	85	1,509	69	Р	I & T	S & NOK
Brenner et al ³⁸	TORONTO	Canada	1997-2002	425	62	910	71	Р&Н	I & T	S
Tse et al ³⁹	HONG KONG	China	2003-2007	1,208	96	1,069	48	Р	I & T	S & NOK
Overall			1985-2010	18,779	84	22,873	78			

AUT-Munich, Arbeit und Technik; CAPUA, Cancer de Pulmon en Asturias; HdA, Humanisierung des Arbeitslebens; EAGLE, Environment and Genetics in Lung cancer Etiology; H, control subjects enrolled from hospitals; HONG KONG, Male lung cancer, occupational exposures, and smoking—A case-control study in Hong Kong; I, interview face to face; ICARE, Investigations Cancers Respiratoires et Environnement; INCO, INCO Copernicus IARC multicenter case-control study of occupational, environment, and lung cancer in Central and Eastern Europe; LLP, Liverpool Lung Project; LUCA, Lung cancer in France; LUCAS, Lung cancer in Stockholm; MONTREAL, Montreal case-control study of environmental causes of lung cancer; OCANZ, Occupational Cancer in New Zealand; N/A, not applicable; NOK, next-of-kin, eg, husband or wife of the study participant; P, control subjects enrolled from the general population; Q, self-administered questionnaire; S, study participant; T, interview over the phone; TORONTO; Toronto lung cancer (casecontrol) study; TURIN/VENETO, Population based case-control study of lung cancer in the city of Turin and in the Eastern part of Veneto Region.

chance.⁴³ We used Stata v. 11.0 for Windows (StataCorp LP, College Station, Texas) for all analyses.

RESULTS

Table 2 summarizes descriptive characteristics of the study participants. Among the controls, smoking was similarly common in firefighters as in nonfirefighters; 74.1% of the firefighters were current or former smokers, and 73.8% of nonfirefighters. However, the percentage of those with more than 20 pack-years among current and former smokers was slightly higher among firefighters; 62.3% among firefighters, compared with 54.8% in nonfirefighters. It was more common in firefighters than in nonfirefighters to have held a job where the lung cancer risk is known to be increased; among the controls, 13.5% of the firefighters, squamous cell carcinoma was the most common lung cancer type, followed by adenocarcinoma and small cell carcinoma.

Overall, we observed no increased risk of lung cancer in firefighters. Before adjustment for smoking, the OR was 1.03 (95% CI 0.77 to 1.38) and after adjusting for smoking 0.95 (95% CI 0.68 to 1.32). Additional adjustment for having ever been employed in a job with established lung cancer risk did not change the OR (Table 3). We found no trend of increasing risk of lung cancer with increasing work duration as a firefighter (P = 0.46 to 0.58) (Table 3). Analyses of lung cancer risk in relation to smoking status showed no increased risk in firefighters when restricted to never smokers (OR = 0.60, 95% CI 0.14 to 2.58), former smokers (OR = 0.75, 95% CI 0.45 to 1.26), or current smokers (OR = 1.18, 95% CI 0.73 to 1.90), though the number of non-smoking firefighters was small. There were only two lung cancer cases in firefighters who had never smoked (Table 4). Analyses

restricted to those who had never had a job where the risk of lung cancer is known to be increased showed no excess risk of lung cancer in firefighters (OR2 = 0.98, 95% CI 0.69 to 1.39) and neither did analyses restricted to ever employed in such an occupation (OR2 = 0.79, 95% CI 0.31 to 1.99) (not shown in table). Analyzing the results by major subtypes of lung cancer showed no association between any of the cell types and work as a firefighter (Table 5). The study-specific ORs for firefighters are shown in Fig. 1. No study showed an increased OR of statistical significance. The risk of lung cancer in firefighters across the studies showed no significant heterogeneity (I^2 0.0%, P = 0.738). Additional analyses including only "General firefighters" showed no increased lung cancer risk (OR3 = 0.88, 95% CI 0.61 to 1.26) (not shown in table).

DISCUSSION

We observed no excess risk of lung cancer in firefighters overall, neither before nor after adjustment for smoking and having ever been employed in a job known to present an excess risk of lung cancer, and there was no significant exposure-response relationship in terms of work duration. Analyses stratified by cell type showed no association between work as a firefighter and any of the major histological cell types of lung cancer. Analyses restricted to never smokers, former smokers, or current smokers showed no increased lung cancer risk in firefighters.

The study covers lifetime occupational information and detailed history of tobacco smoking for almost 15,000 cases and more than 17,000 controls. We have stratified by histology, and examined heterogeneity between studies. However, there were only 86 cases who had ever worked as a firefighter. The statistical power to detect excess risks in the subanalyses was therefore limited, which is evident from the wide CIs.

			Firefighters	(ISCO	5-81)		Nonfire	fighters	
			Cases		Controls		Cases	С	ontrols
Characteristic	Category	No.	% or Mean (SD)	No.	% or Mean (SD)	No.	% or Mean (SD)	No.	% or Mean (SD
Age, years	Mean (SD)	86	62.9 (8.4)	104	61.6 (10.7)	14,662	62.7 (9.0)	17,439	62.3 (9.5)
Study	AUT-Munich	19	22.1	13	12.5	2,639	18.0	2,682	15.4
5	CAPUA	1	1.2	2	1.9	646	4.4	588	3.4
	EAGLE	3	3.5	3	2.9	1,516	10.3	1,599	9.2
	HdA	6	7.0	11	10.6	832	5.7	825	4.7
	HONG KONG	6	7.0	10	9.6	1,188	8.1	1,033	5.9
	ICARE	14	16.3	13	12.5	2,200	15.0	2,728	15.6
	INCO CEE	9	10.5	5	4.8	2,023	13.8	1,987	11.4
	INCO/LLP-UK	5	5.8	12	11.5	276	1.9	561	3.2
	LUCA	3	3.5	4	3.8	294	2.0	290	1.7
	LUCAS	4	4.6	12	11.5	997	6.8	2,265	13.0
	MONTREAL	9	10.5	4	3.8	702	4.8	890	5.1
	OCANZ	3	3.5	5	4.8	207	1.4	410	2.4
	TORONTO	2	2.3	4	3.8	193	1.3	355	2.0
	TURIN/VENETO	2	2.3	6	5.8	949	6.5	1,226	7.0
Age categorized	<45 years	2	2.3	7	6.7	516	3.5	896	5.1
	45-64 years	45	52.3	49	47.1	7,314	49.9	8,383	48.1
	65+ years	39	45.4	48	46.2	6,832	46.6	8,160	46.8
Smoking status	Never smoker	2	2.3	27	26.0	457	3.1	4,571	26.2
(any type of tobacco)	Former smoker	25	29.1	50	48.1	4,927	33.6	7,777	44.6
(Current smoker	59	68.6	27	26.0	9,278	63.3	5,091	29.2
Cigarette pack years	<10	4	4.8	12	15.6	722	5.1	2,852	22.2
(current and former	10-19	15	17.9	14	18.2	1,287	9.1	2,407	18.7
smokers)	20+	65	77.4	48	62.3	12,009	84.5	7,058	54.8
)	Other tobacco	0	0	3	3.9	187	1.3	551	4.3
Years since quitting	2-9 years	11	44.0	9	18.0	2,160	43.8	1,649	21.2
smoking cigarettes	10-20 years	10	40.0	19	38.0	1,699	34.5	2,504	32.2
(former smokers)	21 + years	4	16.0	22	44.0	1,068	21.7	3,624	46.6
Employed in "List A" job	Ever	12	14.0	14	13.5	2,083	14.2	1,588	9.1
Lung cancer cell type	2.00		1.1.0	••	10.0	_,000	12	1,000	2.12
Adenocarcinoma		24	27.9	_		3,832	26.1	_	
Squamous cell carcinoma		34	39.5	_		5,938	40.5	_	
Small cell carcinoma		15	17.4	_		2,263	15.4	_	
Other/unspecified		13	15.1			2,629	17.9	_	

TABLE 2. Descriptive Characteristics of the Male Study Participants by Employment Status as a Firefighter

With regard to possible information bias, there is always some risk of recall bias in case-control studies. However, as only occupations were registered in this study and not more specific information of occupational exposure, the risk of recall bias would probably be low. In all, it is not likely that the absence of association between firefighting and lung cancer found in this study could be attributed to negative recall bias.

It is a limitation that hospital controls were used in some of the studies in SYNERGY, as hospital controls may not adequately reflect the true exposure frequency (ie, occupation as a firefighter) in the population, due to a selection of healthy individuals in firefighting occupation. However, it is not likely that the low risk for lung cancer associated with firefighting found in this study could be explained by an inadequate control group (hospital controls), as the main part of the centers using hospital controls (the INCO study) actually showed an OR above 1.0.

The study showed no evidence of an increased risk of lung cancer, neither in the unadjusted nor adjusted analyses. As the risk estimate changed very little after adjustment for individual lifetime smoking history, it seems unlikely that there could be more than marginal residual confounding from smoking present in the adjusted risk estimates. Important confounding from socioeconomic factors (other than smoking) cannot be entirely ruled out. Firefighters represent an intermediate socioeconomic stratum in the general population, and it does not seem likely that the negative findings in this study could be explained by confounding from socioeconomic status.

Firefighters were identified by occupational codes, which could be a further limitation of our study, as information on their exact tasks and length of employment in such tasks was not available. A limitation is also that we only have duration of employment as a surrogate for exposure. The vast majority (77%) were "General firefighters" but some were "Fire prevention firefighters" or "Aircraft accident firefighters," with possibly lower exposure to fire smoke. However, additional analyses including only "General firefighters" did not change the results. It was more common in firefighters than in nonfirefighters to have held a job where the lung cancer risk is known to be increased. However, analyses restricted to subjects who were never employed in a job with increased lung cancer risk, or restricted to subjects ever employed in such an occupation, did not change the results. When we analyzed the study-specific ORs for firefighters, no study showed an increased OR2 of statistical significance (Fig. 1).

Variable	Exposure Category	Cases	Controls	OR1	95% CI	OR2	95% CI	OR3	95% CI
Firefighter	Never	14,662	17,439	1.0	Reference	1.0	Reference	1.0	Reference
	Ever	86	104	1.03	0.77 - 1.38	0.95	0.68 - 1.32	0.95	0.68-1.32
Duration	<6	32	24	1.56	0.91 - 2.67	1.19	0.65 - 2.15	1.21	0.67 - 2.19
Firefighter (years)	6-21	22	26	1.13	0.64 - 2.00	0.99	0.52 - 1.86	0.97	0.51 - 1.84
	22-32	14	26	0.69	0.36-1.33	0.70	0.32 - 1.50	0.69	0.32 - 1.49
	33+	18	28	0.84	0.46 - 1.53	0.91	0.47 - 1.77	0.92	0.48 - 1.78
	P trend			0.46		0.58		0.58	

TABLE 3. Lung Cancer Relative Risks (OR) and 95% Cl in Relation to Ever and Duration of Employment as a Firefighter

95% CI, 95% confidence interval; OR, odds ratio.

OR1 is adjusted for study and age.

OR2 is in addition adjusted for cumulative cigarette smoking (pack-years) and time since quitting smoking

OR3 is in addition adjusted for ever employment in a List A job (ever/never).

Italic values indicate P trend; <0.05 was considered statistically significant.

	TABLE 4.	Lung Cancer Relative Risks	(OR) a	and 95% CI in Relation to Ever Employment as a Fir	efighter by Smoking Status
--	----------	----------------------------	--------	--	----------------------------

Smoking Status	Firefighter	Cases	Controls	OR	95% CI
Never smoker*	Never	457	4,571	1.0	Reference
	Ever	2	27	0.60	0.14 - 2.58
Former smoker [†]	Never	4,922	7,746	1.0	Reference
	Ever	25	50	0.75	0.45-1.26
Current smoker [‡]	Never	9,278	5,091	1.0	Reference
	Ever	59	27	1.18	0.73-1.90

95% CI, 95% confidence interval; OR, odds ratio.

*OR in never smokers is adjusted for study and age.

[†]OR in former smokers is adjusted for study, age, cumulative cigarette smoking (pack-years), and time since quitting smoking.

[‡]OR in current smokers is adjusted for study, age, and cumulative cigarette smoking (pack-years).

However, the power to detect increased study-specific ORs was very limited due to small numbers of firefighters; therefore, these results should be interpreted with caution.

Most previous studies among firefighters also found no excess risk of lung cancer.^{10–20} Among them, one study of firefighters in the US also examined different cell types of lung cancer and found no increased risk for adenocarcinoma, squamous cell carcinoma, small cell carcinoma, or large cell carcinoma.¹⁰ Three of the studies observed a significantly decreased lung cancer risk in firefighters.^{13,17,18} Findings of a risk deficit are common in working populations and may reflect a selection in relation to work. A healthy worker effect is expected in the case of firefighters, as they need to be healthy to be recruited and to be capable of remaining in the profession.¹⁸ However, some studies have indicated an increased lung cancer risk in firefighters overall or by specific cell type,^{4–8} among them, a case-control study from Turkey,⁴ a case-control study in California,⁸ a cohort study in San Francisco, Chicago and Philadelphia,⁵ a Nordic cohort study,⁷ and a cohort study in Philadelphia.⁶ Only the studies from Turkey and California were controlled for smoking habits. The study from Turkey showed an excess risk of lung cancer in firefighters overall after smoking adjustment, but not for squamous cell carcinoma, and faced low statistical power (10 exposed cases overall and four exposed cases with squamous cell carcinoma).⁴ In the Californian study, firefighters showed an excess risk of nonsmall cell lung cancer after smoking adjustment, but not for other cell types or overall lung cancer (533 exposed cases overall).⁸ In the study of firefighters in San Francisco, Chicago, and Philadelphia, the overall mortality and incidence of lung cancer was increased, based on 1046 and 716 exposed cases, respectively.⁵ Pukkala et al⁷ observed an increased incidence of adenocarcinoma in the lung among Nordic firefighters, but not for squamous cell or small cell carcinoma, and no increased lung cancer risk overall, although an excess was observed in the Danish data. In Philadelphia firefighters, there was an elevated lung

TABLE 5. Lung Cancer Relative Risks (OR) and 95% CI in Relation to Ever Employment as Firefighter by Major Subtype of Lung Cancer

		A	denocaro	rinoma	Squam	ous Cell	Carcinoma	Smal	l Cell C	arcinoma	Ot	her/Unsj	pecified
Fire-Fighter	Controls	Cases	OR2	95% CI									
Never Ever	17,439 104	3,832 24	1.00 1.03	Reference 0.64–1.67	5,938 34	1.00 1.03	Reference 0.66–1.60	2,263 15	1.00 1.03	Reference 0.57–1.87	2,629 13	1.00 0.84	Reference 0.46-1.55

OR2 is adjusted for study, age, cumulative cigarette smoking (pack-years), and time since quitting smoking cigarettes. 95% CI, 95% confidence interval; OR, odds ratio.

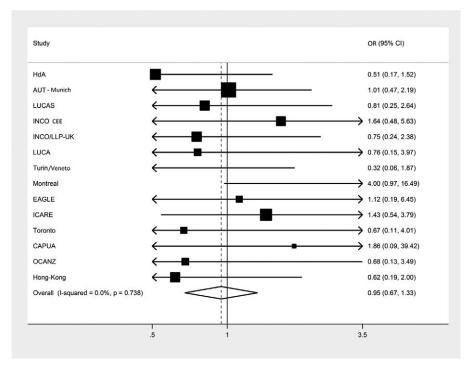


FIGURE 1. Study-specific odds ratios for ever employment as a firefighter compared with never employed as a firefighter in men adjusted for age, smoking status (any type of tobacco), and cigarette pack-years. CI, confidence interval; OR, odds ratio.

cancer mortality overall, although not statistically significant.⁶ Hansen²¹ observed an increased lung cancer mortality in Danish firefighters in the oldest age group, but no increased lung cancer risk overall (based on nine exposed cases), and Heyer et al²² showed an increased lung cancer mortality in the highest age group of Seattle firefighters but no increased overall lung cancer mortality (based on 29 exposed cases).

Most previous studies exploring exposure-response trends found no significant relationship between work duration and lung cancer risk in firefighters,^{5,6,10,16,19,20,44} as in our analysis, whereas a modest positive exposure-response relationship was shown by Daniels et al9 regarding fire-hours and mortality and incidence of lung cancer. This is an important result, stemming from a very large cohort study with the power to detect relatively small overall increases in lung cancer risk, and with the potential for conducting an exposure-response analysis. One study observed no consistent association between lung cancer mortality and duration of employment or an index reflecting exposure, even if the risk was highest in firefighters with the highest exposure.⁴⁴ Only the study of male Massachusetts firefighters described the percentage of smokers, with a slightly lower proportion of current smokers in firefighters (25.7%) than in the control group of police men (28.4%) or men in all other occupations (28.8%), but with the highest proportion of past smokers (46.5% compared with 45.1% and 41.1%, respectively).¹⁵ In SYNERGY, current smoking was less common among the firefighters than among nonfirefighters (26.0% compared with 29.2%, among the controls), with a slightly higher percentage of ever smokers with more than 20 pack-years among firefighters.

A difficulty in interpreting our results, and the overall pattern of findings from previous studies and meta-analyses, is that different exposure patterns have probably been experienced by firefighters in different countries, regions, and periods of time. This point has been extensively addressed by Fritschi and Glass in a recent commentary.⁴⁵ For instance, focusing on one of the most important carcinogens, friable asbestos-containing materials have been widely used in construction in certain urban areas, but less or not at all in others, and opportunities for exposure have varied, as shown by the extreme case of the Twin Tower rescue teams.

In summary, even though firefighters worldwide have a potential for exposure to many different kinds of carcinogens during work, of which some are known lung carcinogens, we observed no excess risk of lung cancer overall or by specific cell type among firefighters. The exposure to carcinogens by inhalation and dermal absorption may certainly vary widely for firefighters between countries depending on work activities and use of protective equipment. In the present pooled study, no study showed an increased lung cancer risk of statistical significance among firefighters.

However, as firefighters may be exposed to a wide variety of chemical compounds during the course of their work, including carcinogenic products such as benzene, arsenic, asbestos, benzo[*a*]-pyrene, cadmium, and silica, it is still important to reduce exposure as much as possible, by safe working practices and the use of adequate protective clothing and respiratory equipment.

CONCLUSION

We found no excess risk of lung cancer overall or for a specific cell type among male firefighters in Europe, Canada, New Zealand, and China, when lifetime history of smoking and exposure to other occupational lung carcinogens was taken into account.

ACKNOWLEDGMENT

The authors wish to thank Mrs Véronique Benhaim-Luzon for pooling the data.

REFERENCES

- 1. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Painting, firefighting, and shiftwork. *IARC Monogr Eval Carcinog Risks Hum.* 2010;98:9–764.
- Austin CC, Wang D, Ecobichon DJ, Dussault G. Characterization of volatile organic compounds in smoke at municipal structural fires. *J Toxicol Environ Health A*. 2001;63:437–458.
- IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Diesel and gasoline engine exhausts and some nitroarenes. *IARC Monogr Eval Carcinog Risks Hum.* 2014;105:9–699.

Copyright © 2016 American College of Occupational and Environmental Medicine. Unauthorized reproduction of this article is prohibited

- Elci OC, Akpinar-Elci M, Alavanja M, Dosemeci M. Occupation and the risk of lung cancer by histologic types and morphologic distribution: a case control study in Turkey. *Monaldi Arch Chest Dis.* 2003;59:183–188.
- Daniels RD, Kubale TL, Yiin JH, et al. Mortality and cancer incidence in a pooled cohort of US firefighters from San Francisco, Chicago and Philadelphia (1950-2009). *Occup Environ Med.* 2014;71:388–397.
- Baris D, Garrity TJ, Telles JL, Heineman EF, Olshan A, Zahm SH. Cohort mortality study of Philadelphia firefighters. *Am J Ind Med.* 2001;39: 463–476.
- Pukkala E, Martinsen JI, Weiderpass E, et al. Cancer incidence among firefighters: 45 years of follow-up in five Nordic countries. *Occup Environ Med.* 2014;71:398–404.
- Tsai RJ, Luckhaupt SE, Schumacher P, Cress RD, Deapen DM, Calvert GM. Risk of cancer among firefighters in California, 1988-2007. *Am J Ind Med.* 2015;58:715–729.
- Daniels RD, Bertke S, Dahm MM, et al. Exposure-response relationships for select cancer and non-cancer health outcomes in a cohort of U.S. firefighters from San Francisco, Chicago and Philadelphia (1950–2009). Occup Environ Med. 2015;72:699–706.
- Demers PA, Checkoway H, Vaughan TL, Weiss NS, Heyer NJ, Rosenstock L. Cancer incidence among firefighters in Seattle and Tacoma, Washington (United States). *Cancer Causes Control.* 1994;5:129–135.
- 11. Tornling G, Gustavsson P, Hogstedt C. Mortality and cancer incidence in Stockholm fire fighters. *Am J Ind Med.* 1994;25:219–228.
- Ma F, Fleming LE, Lee DJ, et al. Mortality in Florida professional firefighters, 1972 to 1999. Am J Ind Med. 2005;47:509–517.
- Ma F, Fleming LE, Lee DJ, Trapido E, Gerace TA. Cancer incidence in Florida professional firefighters, 1981 to 1999. J Occup Environ Med. 2006;48:883–888.
- Bates MN1. Registry-based case-control study of cancer in California firefighters. Am J Ind Med. 2007;50:339–344.
- Kang D, Davis LK, Hunt P, Kriebel D. Cancer incidence among male Massachusetts firefighters, 1987-2003. Am J Ind Med. 2008;51:329–335.
- Ahn YS, Jeong KS, Kim KS. Cancer morbidity of professional emergency responders in Korea. Am J Ind Med. 2012;55:768–778.
- 17. Ide CW. Cancer incidence and mortality in serving whole-time Scottish firefighters 1984–2005. Occup Med (Lond). 2014;64:421–427.
- Amadeo B, Marchand JL, Moisan F, et al. French firefighter mortality: analysis over a 30-year period. Am J Ind Med. 2015;58:437–443.
- Glass DC. Australian Firefighters' Health Study. MONASH Centre for Occupational and Environmental Health. School of Public Health & Preventive Medicine. Faculty of Medicine, Nursing and Health Sciences. Final Report December 10, 2014. Dec 2014. Available at: http://www.coeh. monash.org/downloads/finalreport2014.pdf. Accessed September 3, 2016.
- Ahn YS, Jeong KS. Mortality due to malignant and non-malignant diseases in Korean professional emergency responders. *PLoS One*. 2015;10: e0120305.
- Hansen ES. A cohort study on the mortality of firefighters. Br J Ind Med. 1990;47:805–809.
- Heyer N, Weiss NS, Demers P, Rosenstock L. Cohort mortality study of Seattle fire fighters: 1945-1983. Am J Ind Med. 1990;17:493-504.
- LeMasters GK, Genaidy AM, Succop P, et al. Cancer risk among firefighters: a review and meta-analysis of 32 studies. J Occup Environ Med. 2006; 48:1189–1202.
- 24. Pesch B, Kendzia B, Gustavsson P, et al. Cigarette smoking and lung cancer: relative risk estimates for the major histological types from a pooled analysis of case-control studies. *Int J Cancer*. 2012;131:1210–1219.

- 25. Olsson AC, Gustavsson P, Kromhout H, et al. Exposure to diesel motor exhaust and lung cancer risk in a pooled analysis from case-control studies in Europe and Canada. Am J Respir Crit Care Med. 2011;183:941–948.
- Bigert C, Gustavsson P, Straif K, et al. Lung cancer risk among cooks when accounting for tobacco smoking: a pooled analysis of case-control studies from Europe, Canada, New Zealand, and China. J Occup Environ Med. 2015;57:202–209.
- Brüske-Hohlfeld I, Möhner M, Pohlabeln H, et al. Occupational lung cancer risk for men in Germany: results from a pooled case-control study. Am J Epidemiol. 2000;151:384–395.
- Jöckel KH, Ahrens W, Jahn I, Pohlabeln H, Bolm-Audorff U. Occupational risk factors for lung cancer: a case-control study in West Germany. *Int J Epidemiol.* 1998;27:549–560.
- Consonni D, De Matteis S, Lubin JH, et al. Lung cancer and occupation in a population-based case-control study. Am J Epidemiol. 2010;171:323–333.
- Richiardi L, Boffetta P, Simonato L, et al. Occupational risk factors for lung cancer in men and women: a population-based case-control study in Italy. *Cancer Causes Control*. 2004;15:285–294.
- Stücker I, Hirvonen A, de Waziers I, et al. Genetic polymorphisms of glutathione S-transferases as modulators of lung cancer susceptibility. *Carcinogenesis*. 2002;23:1475–1481.
- Guida F, Papadopoulos A, Menvielle G, et al. Risk of lung cancer and occupational history: results of a French population-based case-control study, the ICARE study. J Occup Environ Med. 2011;53:1068–1077.
- López-Cima MF, González-Arriaga P, García-Castro L, et al. Polymorphisms in XPC, XPD, XRCC1, and XRCC3 DNA repair genes and lung cancer risk in a population of northern Spain. *BMC Cancer*. 2007;7:162.
- Scélo G, Constantinescu V, Csiki I, et al. Occupational exposure to vinyl chloride, acrylonitrile and styrene and lung cancer risk (Europe). *Cancer Causes Control*. 2004;15:445–452.
- Gustavsson P, Jakobsson R, Nyberg F, Pershagen G, Järup L, Schéele P. Occupational exposure and lung cancer risk: a population-based casereferent study in Sweden. Am J Epidemiol. 2000;152:32–40.
- Corbin M, McLean D, Mannetje A, et al. Lung cancer and occupation: a New Zealand cancer registry-based case-control study. *Am J Ind Med.* 2011;54:89–101.
- Ramanakumar AV, Parent ME, Siemiatycki J. Risk of lung cancer from residential heating and cooking fuels in Montreal, Canada. Am J Epidemiol. 2007;165:634–642.
- Brenner DR, Boffetta P, Duell EJ, et al. Previous lung diseases and lung cancer risk: a pooled analysis from the International Lung Cancer Consortium. Am J Epidemiol. 2012;176:573–585.
- Tse LA, Yu IT, Qiu H, Au JS, Wang XR. Occupational risks and lung cancer burden for Chinese men: a population-based case-referent study. *Cancer Causes Control*. 2012;23:121–131.
- International Labour Office. International Standard Classification of Occupations. 2nd. Geneva, Switzerland: International Labour Office; 1968.
- Ahrens W, Merletti F. A standard tool for the analysis of occupational lung cancer in epidemiologic studies. Int J Occup Environ Health. 1998;4:236–240.
- 42. Mirabelli D, Chiusolo M, Calisti R, et al. Database of occupations and industrial activities that involve the risk of pulmonary tumors [Article in Italian]. *Epidemiol Prev.* 2001;25:215–221.
- Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560.
- Guidotti TL. Mortality of urban firefighters in Alberta, 1927–1987. Am J Ind Med. 1993;23:921–940.
- Fritschi L, Glass DC. Firefighters and cancer: where are we and where to now? Occup Environ Med. 2014;71:525–526.