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ABSTRACT

Several epidemiologic studies indicated an increased risk of lung cancer among welders. We took advantage of a large collection of lung cancer cases and controls with occupational and smoking histories from the SYNERGY project to assess welding as a risk factor for developing lung cancer. The database comprises 15,483 male lung cancer cases and 18,388 controls from 16 studies in Europe, Canada, China, and New Zealand, conducted between 1985 and 2010. Odds ratios (OR) and 95% confidence intervals (95%CI) for lung cancer were estimated, adjusted for smoking and other confounders. Overall, 568 cases and 427 controls had ever worked as a welder, and 1,994 cases and 1,930 controls had ever worked in occupations with occasional welding. Welding was associated with an elevated OR for lung cancer (welders: 1.44, 95%CI: 1.25, 1.67; occasional welding: 1.19, 95%CI: 1.10, 1.28) and increased with duration of employment. Regular welding showed a stronger association with lung cancer in never and light smokers (0-<10 packyears: 1.96, 95%CI: 1.37, 2.79) and with squamous cell cancer and small cell lung cancer than with adenocarcinoma. Our findings contribute to the increasing evidence that welding is associated with an increased risk of lung cancer.

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Abbreviations: AdCa, adenocarcinoma; CI, conficence interval; IARC, International Agency for Research on Cancer; ISCO-68, International Standard Classification of Occupations, Revision 1968; ISIC, International Standard Industrial Classification; OR, odds ratio; SCLC, small cell lung cancer; SqCC, squamous cell carcinoma;

Running head: Welding and lung cancer

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Worldwide several millions of workers are exposed to welding fumes while working as welders or in occupations or workplaces in which joining of metal parts are commonly performed. In 1990, the International Agency for Research on Cancer (IARC) classified welding fumes as a possible human carcinogen (Group 2B) (1). New evidence for an excess lung cancer risk in welding has been found in several studies, including a recent meta-analysis and a large record-linkage study (2, 3). Research gaps and recommendations have been discussed by Ward *et al.* (4).

Welding fume is a complex mixture of particles containing metals and gases that are formed during the burning of electrodes and heating of the base metal. The particle mass concentration is strongly correlated with iron and manganese as major constituents of steel (5), but moderately with chromium and nickel, which are added to the production of stainless steel (6). Ship-building is a prominent example for welding of large parts of mild steel with gas metal arc welding and is associated with high exposure to particles and lower exposure to chromium and nickel as compared to settings using stainless steel (6, 7).

Although the association of welding with lung cancer has been repeatedly investigated, a causal association between welding and lung cancer has not yet been firmly established, except for stainless steel welders. Further questions remain, for example the contribution that welding makes to the etiology of the different subtypes of lung cancer and how welding interacts with smoking in lung cancer development. Smoking is more closely associated with squamous cell cancer (SqCC) and small cell cancer of the lung (SCLC) than with adenocarcinoma (AdCa) (8).

We took advantage of a large collection of lung cancer cases and controls with occupational and smoking histories from the SYNERGY project to explore welding as a risk factor for developing lung cancer. More information about SYNERGY has been previously published (8, 9) and is available at http://synergy.iarc.fr.

MATERIALS AND METHODS

Study population

The pooled dataset for this analysis comprised 15,483 male cases and 18,388 male controls that were enrolled in 16 studies between 1985 and 2010 (supplementary Table S1). We excluded women due to the low prevalence of welders among them; only 32 women had ever been employed in welding occupations. The majority of controls were recruited from the general population (81.6%). Occupational and smoking histories were mainly assessed in face-to-face interviews (80.6%). The majority of subjects were alive at the time of interview (87.9%). The Ethics Committees of the individual studies approved the realization of the study, as did the IARC Institutional Review Board.

Assessment of welding activities

Occupations were coded according to the International Standard Classification of Occupations, Rev. 1968 (ISCO-68) (10). Industries were classified according to the International Standard Industrial Classification (ISIC) Rev. 2 (11). Using the 5-digit ISCO-68 codes (supplementary Table S2), two classifications of welding-related occupations were considered: men who ever worked for at least one year as a welder, and men ever working in occupations with potential welding activities (further referred to as ‘occasional welding’).

Occasional welding was assessed by expert rating of job titles (B.K., B.P., H.K., R.V., and S.P.) and excluded men who ever worked as a regular welder. We further stratified both groups by industry where welding is commonly applied (ship building and repair, construction, manufacture of machines and related equipment, manufacture of motor vehicles and repair of transport equipment, others) (supplementary Table S3).

Statistical analysis

The odds ratio (OR) for working as a welder or in occasional welding and 95% confidence intervals (95%CI) were estimated by unconditional logistic regression. OR1 was adjusted for age (log-transformed) and study centers (22 centers), OR2 was additionally adjusted for smoking (log(packyears+1), time-since-quitting smoking cigarettes (current smokers, ever other types of tobacco only, stopping smoking 2-7, 8-15, 16-25, 26+ years before interview/diagnosis, never smokers)). The full adjustment (OR3) additionally considered employment in occupations at-risk for lung cancer excluding welding-related occupations ("List A" jobs (12, 13)). Subjects, who had never worked in welding-related occupations, comprised the reference group. We defined light smokers as subjects who smoked less than 10 packyears. Tests for linear trend were performed for the OR as a function of duration of employment and time since last employment as a welder. We estimated the lung cancer risk for regular or occasional welding as ever held and longest-held occupation, stratified by smoking and subtype of lung cancer, in subjects who never worked in a "List A" job and in workers ever employed in a 'blue-collar' occupation (with 7, 8, or 9 as first digit of their job-title code according to ISCO-68). Sensitivity analyses were performed by type of controls and for workers who started welding after 1979, when measures for the improvement of occupational hygiene became implemented. Meta-regression models with random effects

were applied to estimate ORs for the combined and individual studies, and heterogeneity between studies was assessed by I^2 statistics (Comprehensive Meta-Analysis Version 2.2.027, Biostat, Englewood, NJ). All other analyses were performed with SAS software, version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Study population

Table 1 characterizes the study groups. A total of 568 male lung cancer cases (3.7%) and 427 controls (2.3%) ever worked as a welder. A large fraction of 40.1% of welders among the controls reported this occupation as longest-held job, with a median of 27 years (interquartile range 18-35 years). Additional 1994 cases (12.9%) and 1930 controls (10.5%) were identified as having worked in occupations with occasional welding. A similar fraction of 36.1% had occupation as longest-held job (median of 31 years, interquartile range 23-38 years). More welders ever smoked or worked in other at-risk occupations as compared to men who had never worked in welding-related occupations.

Lung cancer risk among welders and in occasional welding

If not otherwise stated, we report the fully adjusted risk estimates. Figure 1 shows a meta-OR of 1.42 (95%CI: 1.23, 1.66) for ever working as a welder with low heterogeneity between individual studies (I^2=29.6%, P=0.10) and of 1.17 (95%CI: 1.08, 1.27) for occasional welding (I^2=20.9%, P =0.19). Table 2 presents the risk estimates from the pooled analysis. Working as a welder was associated with an increased lung cancer risk (ever welder: 1.44, 95%CI: 1.25, 1.67, longest held job: 1.50 (95%CI: 1.20, 1.88). Occasional welding was also associated with

an elevated lung cancer risk (ever: 1.19, 95%CI: 1.10, 1.28). The risk estimates remained increased when restricted to men never working in a "List A" job or to blue-collar workers (welder as longest held occupation: 1.63, 95%CI: 1.26, 2.11, and 1.39; 95%CI: 1.11, 1.73, respectively). ORs were 1.53 (95%CI: 1.29, 1.82) when restricted to population controls, 1.10 (95%CI: 0.84, 1.44) in studies with hospital controls, and 1.31 (95%CI: 0.68, 2.58) for having started working after 1979 (supplementary Table S4).

Lung cancer risk by industry

Welding in the construction industry showed an increased lung cancer risk (ever welder: 1.47, 95%CI: 1.22, 1.78; ever occasional welding: 1.21, 95%CI: 1.09, 1.33). We estimated an elevated risk for ever working as welder in ship building and repair (1.53, 95%CI: 1.06, 2.21), but not for occasional welding (0.90, 95%CI: 0.68, 1.20). The estimates of the lung cancer risk in the motor vehicle and motor bike production were comparatively low, for example 0.62 (95%CI: 0.28, 1.36) for welding as the longest held job. More results are shown in Table 3.

Lung cancer risk by duration of employment in regular or occasional welding

Short-term exposure (<3 years of welding) was associated with a relative lung cancer risk of 1.14 (95%CI: 0.80, 1.61) in regular welders and of 1.13 (95%CI: 0.94, 1.34) in occasional welding (Table 4). The risks increased with longer duration of welding. Long-term exposure (>25 years of welding) was associated with an OR of 1.77 (95%CI: 1.31, 2.39) in welders and of 1.40 (95%CI: 1.21, 1.62) in occasional welders. We did not observe a risk reduction with increasing time since last welding (data not shown).

Lung cancer risk by histological subtype and smoking

Table 5 shows the risk estimates of ever working as a welder for the major subtypes of lung cancer (AdCa 1.23, 95%CI: 0.99, 1.53, SqCC 1.58, 95%CI: 1.32, 1.89, SCLC 1.41, 95%CI: 1.09, 1.82). Among never or light smoking welders, the estimates of the risk for SqCC and SCLC were increased more strongly, but were based on small numbers (never smokers: AdCa 1.89, 95%CI: 0.79, 4.52, SqCC 3.01, 95%CI: 1.07, 8.49, SCLC 4.45, 95%CI: 1.03, 19.18). This pattern was not observed among never-smoking occasional welders.

DISCUSSION

Analyses of a large database of occupational and smoking histories from about 33,900 men within the framework of the SYNERGY project, we demonstrated that welding is associated with an increased lung cancer risk. A meta-analysis of 66 epidemiological studies revealed a 26% excess of lung cancer risk among welders (2). Two studies of which were also part of our analysis (14, 15). A large record-linkage study in the Nordic countries estimated a 33% increased lung cancer incidence in welders, although this study did not adjust for smoking (3). The adjustment for smoking habits suggests that confounding by tobacco smoking may explain about 20% of the increase in lung cancer risk in welders.

Welding is a common task in many occupations, where joining of metal parts is occasionally performed. In order to provide better evidence for lung cancer risks in welding, we investigated welders and workers in occupations with potential welding activities separately. In the pooled analysis of 16 case-control studies, we observed a 44% smoking-adjusted increase in risk for ever working as a welder and a 19% increase for occasional welding, but the risks were lower in studies with hospital controls. This estimate showed only minor

changes when we restricted the analysis to blue-collar workers or subjects not working in other at-risk occupations. The risk increased up to 77% for welders worked more than 25 years.

There is a variety of welding techniques with a wide range of emissions of particles and metals (7). The welding technique and the metal content of the electrodes are important determinants of the composition of welding fumes (6). Flux-cored arc welding is frequently used for joining large metal parts of mild steel, e.g. in shipyards, leading to high level of particle exposure and comparatively low concentrations of chromium and nickel. We found a significantly increased risk for regular welders in ship building but not for occasional welding. The finding that lung cancer risk is also increased among welders in shipyards where predominantly mild steel is used and exposure to particulates is high indicates that the risk is not restricted to stainless steel welding. Overall, we did not observed a significantly increased lung cancer risk of welding in the manufacture of motor vehicles. Welding of car parts has been subject to technological improvements, such as automated laser welding in enclosed spaces, whereas the joining of large ship parts is still performed with high-emission technologies (2).

A limitation of this pooled analysis is that information on the welding process or on the specific nature of workplace exposures was not available in this job title-based analysis. Still, the job title of "welder" is one that carries a strong likelihood of exposure to some form of welding fumes. There is certainly an opportunity for workers with other job titles to engage in or be in proximity to welding operations. We attempted to identify the main occupations in our listing of tasks with occasional welding activities. These workers comprise a larger group

compared to subjects that worked as a regular welder (16). We cannot fully exclude misclassification of exposure, especially of occasional welders, where several workers might not have performed welding. On the other hand, it is possible that some workers in our "unexposed" category also had been exposed to welding fumes. However, this would only represent a very small fraction of the reference group and would tend to attenuate the risk estimates toward unity.

When analysing the risk in blue-collar workers only, we observed somewhat lower but still elevated lung cancer risks in welding. Welders worked more frequently in other occupations known to entail an increased lung cancer risk. However, the risk estimates did not change when we adjusted for working in "List A" jobs, or when we restricted the analysis to men who never worked in other at-risk occupations. The U.S. National Institute of Occupational Safety and Health concluded in 1988 that there is an elevated risk of lung cancer among welders that cannot be completely accounted for by smoking or asbestos exposure (17). Exposure to asbestos can occur during welding, especially in shipyards (1). The risk estimate was lower for welders who started working after 1979, when concerns about the health risks of asbestos initiated the implementation of protective measures and a decline in asbestos consumption (18). Several studies adjusted for exposure to asbestos, including four studies that were part of our pooled analysis (14, 15, 19, 20). However, the inclusion of life-time exposure to asbestos into the model did not influence the estimate of the relative lung cancer risk among welders in the INCO study (19). Exposure to asbestos was usually assessed with categorical variables based on expert rating. Personal measurements of asbestos fibres in the breathing zone of welders are rarely available. We adjusted for other at-risk occupations except welding and considered welding as a complex exposure circumstance, where exposure

to asbestos could be an integral part. Asbestos could be used as filler of cylinders with acetylene gas or being part of certain covered rod electrodes. Asbestos fibres are not stable at the high temperatures during welding (21). Asbestos-containing materials were used for heat protection, and, for example, to cover the weld in order to delay the cooling process. Exposure to asbestos is further possible when repairing metal parts with asbestos insulation or as bystander. Elevated mesothelioma risks among welders have been reported (22). The asbestos burden in the lungs of welders with mesothelioma was lower than in cases from the asbestos manufacturing industry or insulation sector (23). Taking this together, welding fume may exert a lung cancer risk that cannot be sufficiently explained by asbestos. Future research should consider types of welding and assessment of specific exposures by different welding scenarios.

Welders were more frequently smokers, as compared to the reference group and adjustment for smoking attenuated the risk estimates. Residual confounding by smoking can be a methodological problem. The detailed SYNERGY data allowed a detailed adjustment for smoking, and the large size of SYNERGY allowed a stratified analysis by smoking status. The elevated odds ratios observed in never and light smokers are in line with a former report from the MONTREAL study (20) and support a direct effect of welding on lung cancer. The higher risk in never or light smokers might reflect the limited capacity of the lung to deal with exposure to pulmonary carcinogens.

We found a stronger association of welding with SqCC and SCLC than with AdCa. This different association was also observed in other studies (24, 25). Also individual SYNERGY studies (14, 15, 19, 24, 26, 27) have reported on histological subtypes of lung cancer but were

based on smaller numbers (20, 28, 29). The same pattern was reported for exposure to pulmonary carcinogens in uranium miners (30) and was even more pronounced in the association of smoking with lung cancer (8).

Summarizing, our findings contribute to the increasing evidence that welding is associated with an increased lung cancer risk. The lung cancer risk of regular welders was higher than for men ever worked in an occupation with occasional welding. We observed a slightly stronger risk in never and light smokers and a trend with duration of employment in welding-related jobs, as well as a stronger association of welding with SqCC and SCLC than with AdCa. The findings from this investigation support the need for additional research to identify the agent(s) responsible for possible lung cancer risks.

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Table 1. Distribution of various characteristics of the study population according to case-control and welding exposure status, SYNERGY, 1985-2010

Characteristics	Welders				Occasional welding tasks				Never worked in welding-related occupations			
	Controls		Cases		Controls		Cases		Controls		Cases	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
No. of participants	427	2.3	568	3.7	1,930	10.5	1,994	12.9	16,031	87.2	12,921	83.5
Age [years][a]	62 (55-68)		61 (55-68)		62 (55-68)		62 (55-68)		64 (56-70)		64 (57-70)	
Packyears in smokers[a]	25 (14-40)		39 (28-54)		24 (11-38)		37 (26-50)		24 (11-40)		40 (27-56)	
Duration of employment in welding[a]	10 (3-22)		12 (4-26)		10 (3-25)		10 (3-27)		0		0	
Smoking status of cigarettes												
Never smokers	78	18.3	15	2.6	408	21.1	48	2.4	4,391	27.4	439	3.4
Former smokers	194	45.4	185	32.6	901	46.7	704	35.3	6,995	43.6	4,533	35.1
Current smokers	153	35.8	366	64.4	577	29.9	1,228	61.6	4,268	26.6	7,805	60.4
Other types of tobacco only	2	0.5	2	0.4	44	2.3	14	0.7	377	2.4	144	1.1
"List A" occupations except welding tasks												
Never	314	73.5	394	69.4	1,630	84.5	1,599	80.2	14,765	92.1	11,324	87.6
Ever	113	26.5	174	30.6	300	15.5	395	19.8	1,266	7.9	1,597	12.4
Histological subtype												
Adenocarcinoma		-	132	23.2		-	510	25.6		-	3,339	25.8
Squamous cell cancer		-	264	46.5		-	812	40.7		-	5,294	41.0
Small cell lung cancer		-	92	16.2		-	314	15.7		-	2,005	15.5
Other or mixed		-	80	14.1		-	358	18.0		-	2,283	17.7

[a] Values are expressed as median (interquartile range).

Table 2. Lung cancer risk among workers in welding-related occupations, SYNERGY, 1985-2010

Occupations	No. Controls	No. Cases	OR1[a]	OR2[b]	CI	OR3[c]	CI
Reference group[d]	16,031	12,921	1.00	1.00		1.00	
Welders							
Ever	427	568	1.69	1.45	1.25, 1.68	1.44	1.25, 1.67
Longest held occupation	172	246	1.78	1.48	1.19, 1.86	1.50	1.20, 1.88
Occasional welding tasks							
Ever	1,930	1,994	1.27	1.18	1.10, 1.28	1.19	1.10, 1.28
Longest held occupation	697	746	1.37	1.31	1.16, 1.48	1.32	1.17, 1.49
Never employed in a "List A" job							
Never worked in welding-related occupations	14,765	11,323	1.00	1.00			
Welders							
Ever	314	394	1.70	1.46	1.23, 1.74		
Longest held occupation	129	186	1.92	1.63	1.26, 2.11		
Occasional welding tasks							
Ever	1,630	1,599	1.28	1.18	1.09, 1.29		
Longest held occupation	623	627	1.37	1.27	1.11, 1.45		
Ever employed in a "blue collar" job							
Never worked in welding-related occupations	10,289	9,796	1.00	1.00		1.00	
Welders							
Ever	427	568	1.45	1.32	1.14, 1.53	1.33	1.15, 1.54
Longest held occupation	172	246	1.55	1.36	1.09, 1.71	1.39	1.11, 1.73
Occasional welding tasks							
Ever	1,930	1,994	1.08	1.06	0.98, 1.15	1.07	0.99, 1.16
Longest held occupation	697	746	1.16	1.18	1.04, 1.33	1.20	1.06, 1.36

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

[a] OR1 is adjusted for log(age) and study centers.

[b] OR2 is additionally adjusted for log(packyears+1), time-since-quitting smoking cigarettes (current smokers, ever other types of tobacco only,

stopping smoking 2-7, 8-15, 16-25, 26+ years before interview/diagnosis, never smokers).
[c] OR3 is additionally adjusted for ever working in a "List A" job except welding.
[d] Defined as subjects, who had never worked in welding-related occupations.

Table 3. Lung cancer risk among workers in welding-related occupations by industry, SYNERGY, 1985-2010

Industries	Ever-held job						Longest held job					
	No. Controls	No. Cases	OR1[a]	OR2[b]	OR3[c]	CI	No. Controls	No. Cases	OR1[a]	OR2[b]	OR3[c]	CI
Reference group[d]	16,031	12,921	1.00	1.00	1.00		16,031	12,921	1.00	1.00	1.00	
Welders												
Ship building and repair	59	93	1.99	1.57	1.53	1.06, 2.21	15	33	2.50	1.73	1.53	0.89, 3.41
Construction and related building services	240	336	1.78	1.50	1.47	1.22, 1.78	32	46	1.67	1.31	1.33	0.81, 2.20
Manufacture of machines, equipment, appliances	271	352	1.65	1.40	1.40	1.17, 1.68	57	104	2.38	2.08	2.11	1.45, 3.08
Manufacture of motor vehicles and motor bikes	93	102	1.56	1.33	1.30	0.94, 1.80	23	12	0.75	0.62	0.62	0.28, 1.36
Repair of transport equipments	101	136	1.70	1.51	1.51	1.12, 2.03	12	16	1.49	1.14	1.10	0.49, 2.46
Others	13	22	1.98	2.27	2.31	0.99, 5.39	33	35	1.29	1.25	1.27	0.74, 2.20
Occasional welding tasks												
Ship building and repair	132	132	1.26	1.17	0.90	0.68, 1.20	47	45	1.77	1.73	1.32	0.78, 2.23
Construction and related building services	1,152	1,238	1.36	1.24	1.21	1.09, 1.33	216	244	1.53	1.44	1.43	1.21, 1.67
Manufacture of machines, equipment,	739	734	1.20	1.17	1.14	1.01, 1.28	132	136	1.33	1.30	1.28	1.02, 1.60

appliances												
Manufacture of motor vehicles and motor bikes	264	228	1.11	0.98	0.95	0.77, 1.16	69	60	1.28	1.04	1.03	0.71, 1.49
Repair of transport equipments	843	835	1.22	1.14	1.11	0.99, 1.24	170	206	1.23	1.20	1.18	0.98, 1.44
Others	112	101	1.05	0.89	0.91	0.67, 1.24	63	55	1.08	0.99	1.01	0.66, 1.54

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

[a] OR1 is adjusted for log(age) and study centers.

[b] OR2 is additionally adjusted for log(packyears+1), time-since-quitting smoking cigarettes (current smokers, ever other types of tobacco only, stopping smoking 2-7, 8-15, 16-25, 26+ years before interview/diagnosis, never smokers).

[c] OR3 is additionally adjusted for ever working in a "List A" job except welding.

[d] Defined as subjects, who had never worked in welding-related occupations.

Table 4. Lung cancer risk of welding-related occupations by histological subtype and duration of employment, SYNERGY, 1985-2010

		All cases			AdCa			SqCC			SCLC		
Duration	**No. Controls**	**No.**	**OR3[a]**	**CI**	**No.**	**OR3[a]**	**CI**	**No.**	**OR3[a]**	**CI**	**No.**	**OR3[a]**	**CI**
Reference group[c]													
	16,031	12,921	1.00		3,313	1.00		5,226	1.00		1,979	1.00	
Welders													
	427	568	1.44	1.25, 1.67	132	1.23	0.99, 1.53	264	1.58	1.32, 1.89	92	1.41	1.09, 1.82
1-<3	84	82	1.14	0.80, 1.61	18	0.84	0.49, 1.45	41	1.38	0.90, 2.11	14	1.25	0.67, 2.35
3-<10	124	171	1.46	1.26, 1.91	39	1.14	0.77, 1.68	77	1.62	1.16, 2.25	32	1.49	0.96, 2.32
10-≤ 25	129	167	1.38	1.06, 1.79	41	1.26	0.85, 1.87	76	1.34	0.97, 1.85	28	1.30	0.82, 2.07
> 25	90	148	1.77	1.31, 2.39	34	1.31	0.85, 2.02	70	1.71	1.19, 2.46	18	1.20	0.69, 2.11
P[b]				<0.0001			0.1041			0.0002			0.1311
Occasional welding tasks													
	1,930	1,994	1.19	1.10, 1.28	510	1.22	1.09, 1.37	812	1.14	1.03, 1.25	314	1.09	0.94, 1.25
1-<3	323	333	1.13	0.94, 1.34	93	1.26	0.98, 1.62	141	1.17	0.93, 1.48	49	0.98	0.70, 1.37
3-<10	642	638	1.11	1.00, 1.24	153	1.11	0.91, 1.35	241	0.90	0.76, 1.06	117	1.05	0.84, 1.31
10-≤25	485	487	1.16	1.00, 1.34	131	1.18	0.95, 1.46	207	1.14	0.94, 1.37	75	1.05	0.80, 1.38
> 25	480	536	1.40	1.21, 1.62	133	1.28	1.03, 1.58	223	1.37	1.13, 1.65	73	1.15	0.87, 1.51
P[b]				<0.0001			0.0193			0.0011			0.5687

Abbreviations: AdCa, Adenocarcinoma; CI, 95% confidence interval; OR, odds ratio; SCLC, Small cell lung cancer; SqCC, Squamous cell cancer.
[a] OR3 is adjusted for log(age), study centers, log(packyears+1), time-since-quitting smoking cigarettes (current smokers, ever other types of tobacco only, stopping smoking 2-7, 8-15, 16-25, 26+ years before interview/diagnosis, never smokers), and for ever working in a "List A" job.
[b] Trend-test P values were computed by entering the continuous variable duration of employment into the model.
[c] Defined as subjects, who had never worked in welding-related occupations.

Table 5. Lung cancer risk of welding-related occupations by histological subtype and smoking, SYNERGY, 1985-2010

		All cases			AdCa			SqCC			SCLC		
Occupations	**No. Controls**	**No.**	**OR3[a]**	**CI**	**No.**	**OR3[a]**	**CI**	**No.**	**OR3[a]**	**CI**	**No.**	**OR3[a]**	**CI**
Reference group[b]													
	16,031	12,921	1.00		3,313	1.00		5,226	1.00		1,979	1.00	
Welders													
	427	568	1.44	1.25, 1.67	132	1.23	0.99, 1.53	264	1.58	1.32, 1.89	92	1.41	1.09, 1.82
Smoking status													
Never	78	15	2.34	1.31, 4.17	6	1.89	0.79, 4.52	4	3.01	1.07, 8.49	2	4.45	1.03, 19.2
Ever	349	553	1.33	1.14, 1.54	126	1.12	0.90, 1.41	260	1.49	1.24, 1.78	90	1.31	1.01, 1.70
Packyears													
0-<10	146	47	1.96	1.37, 2.79	12	1.37	0.74, 2.52	18	2.25	1.30, 3.91	7	2.28	0.99, 5.29
10-35	174	189	1.19	0.95, 1.49	45	1.07	0.75, 1.52	86	1.35	1.01, 1.79	35	1.36	0.91, 2.04
≥35	107	332	1.34	1.06, 1.69	75	1.15	0.84, 1.59	160	1.50	1.16, 1.96	50	1.12	0.78, 1.62
Occasional welding tasks													
	1,930	1,994	1.19	1.10, 1.28	510	1.22	1.09, 1.37	812	1.14	1.03, 1.25	314	1.09	0.94, 1.25
Smoking status													
Never	408	48	1.31	0.95, 1.81	25	1.16	0.76, 1.78	8	1.13	0.54, 2.37	2	0.76	0.18, 3.19
Ever	1,522	1,946	1.15	1.07, 1.25	485	1.19	1.06, 1.34	804	1.11	1.00, 1.23	312	1.06	0.92, 1.23
Packyears													
0-<10	784	166	1.20	0.99, 1.45	62	1.31	0.98-1.74	53	1.02	0.74, 1.41	22	1.14	0.70, 1.85
10-35	699	767	1.20	1.07, 1.35	190	1.16	0.97, 1.39	313	1.20	1.03, 1.40	122	1.09	0.87, 1.36
≥35	447	1,061	1.09	0.96, 1.24	258	1.16	0.96, 1.39	446	1.06	0.91, 1.23	170	1.01	0.82, 1.24

Abbreviations: AdCa, Adenocarcinoma; CI, 95% confidence interval; OR, odds ratio; SCLC, Small cell lung cancer; SqCC, Squamous cell cancer.

[a] OR3 is adjusted for log(age), study centers, log(packyears+1), time-since-quitting smoking cigarettes (current smokers, ever other types of tobacco only, stopping smoking 2-7, 8-15, 16-25, 26+ years before interview/diagnosis, never smokers), and for ever working in a "List A" job. Smoking variables were omitted when analyzing never smokers.

[b] Defined as subjects, who had never worked in welding-related occupations.

Figure 1. Study-specific odds ratios (OR3s) with 95% confidence interval (CI) for ever working as a welder (A) or in occasional welding (B) compared with men who never worked in welding-related occupations adjusted for log(age), study center, log(packyears+1), time-since-quitting smoking cigarettes, and for ever working in a "List A" occupation except welding

WEB MATERIAL

Table S1. Characteristics of the studies selected for the pooled analysis of lung cancer risk among male welders, SYNERGY, 1985-2010

Study	Country	Recruitment period	Job periods	Cases		Controls		Source of controls	Type of interview
				No.[c]	RR %[b]	No.[c]	RR %[b]		
AUT	Germany	1990–1995	1931–1995	2,659	76	2,702	41	P	Face-to-face
HdA	Germany	1988–1993	1926–1993	839	69	838	68	P	Face-to-face
EAGLE	Italy	2002–2005	1931–2005	1,536	87	1,617	72	P	Face-to-face
TURIN/VENETO	Italy	1990–1994	1922–1994	955	79	1,249	80	P	Face-to-face
ROME	Italy	1993–1996	1926–1996	294	74	264	63	H	Face-to-face
LUCA	France	1989–1992	1926–1992	307	98	302	98	H	Face-to-face
PARIS	France	1988–1992	1923–1992	161	95	219	95	H	Face-to-face
ICARE	France	2001–2007	1937–2007	2,243	80	2,749	76	P	Face-to-face[a]
CAPUA	Spain	2000–2010	1926–2010	774	91	712	96	H	Face-to-face
MORGEN	NL	1993–1997	1945–1997	41	N/A	111	N/A	P	Self-administered questionnaire
INCO	CZ	1999–2002	1935–2002	235	94	294	80	H	Face-to-face
INCO	Hungary	1998–2001	1931–2001	313	90	250	100	H	Face-to-face
INCO	Poland	1998–2002	1936–2002	551	88	574	88	H/P	Face-to-face
INCO	Slovakia	1998–2002	1935–2002	288	90	236	84	H	Face-to-face
INCO	Romania	1998–2002	1936–2002	141	90	152	99	H	Face-to-face
INCO	Russia	1998–2001	1931–2001	521	96	503	90	H	Face-to-face
INCO (LLP)	UK	1998–2005	1932–2005	281	78	573	84	P	Face-to-face
LUCAS	Sweden	1985–1990	1923–1990	1,018	87	2,309	85	P	Mail, telephone[a]
OCANZ	NZ	2003–2009	1941–2009	212	53	417	48	P	Face-to-face, telephone[a]
MONTREAL	Canada	1996–2002	1933–2002	714	85	895	69	P	Face-to-facea
TORONTO	Canada	1997–2002	1929–2002	198	62	371	84/60	H/P	Face-to-face
HONG KONG	China	2003-2007	1931–2007	1,202	96	1,051	48	P	Face-to-face, telephone[a]
Overall		1985–2010	1922–2010	15,483	82	18,388	74		

Abbreviations: CZ, Czech Republic; H, hospital controls; N/A, not applicable; NL, Netherlands; NZ, New Zealand; P, population controls; RR, response rate.
[a] Interviews also with a next of kin.
[b] Response rate was reported for both genders.
[c] Men with complete occupational and smoking history.

Table S2. Classification of welders and occupations with potential welding activities according to the International Standard Classification of Occupations (ISCO) 1968, SYNERGY, 1985-2010

ISCO Code	Description
Welders	
87200	Welders
87210	Gas and electric welders (general)
87215	Gas welders
87220	Electric arc welders (hand)
87225	Electric arc welders (machine)
87230	Thermite arc welders
87235	Resistance welders
Occupations with potential welding activities	
87105	Plumbers
87110	Pipe fitters
87120	Gas pipe fitters
87130	Marine pipe fitters
87140	Aircraft pipe and tube fitters
87190	Other plumbers and pipe fitters
87310	Sheet-metal workers
87350	Boilersmith
87360	Ornamental sheet-metal workers
87370	Vehicle sheet-metal workers
87380	Aircraft sheet-metal workers
87390	Other sheet-metal workers
87400	Structural metal preparers and erectors
87430	Structural steel workers (workshop)
87440	Constructional steel erectors
87450	Metal shipwright
87490	Other structural metal preparers and erectors
95350	Metal roofers
84185	Airframe fitter-assemblers
84190	Other machinery fitters and machine assemblers
84910	Machinery mechanics (general)
84920	Diesel engine mechanics (except motor vehicle)
84955	Agricultural machinery mechanics
84300	Motor-vehicle mechanics
84320	Automobile mechanics
84330	Motor-truck mechanics
84340	Motor-cycle mechanics
84390	Other motor-vehicle mechanics
84400	Aircraft engine mechanics
84410	Aircraft engine mechanics (general)
84420	Aircraft engine service mechanics

84490	Other aircraft engine mechanics
87290	Other welders and flame-cutters
72700	Metal drawers and extruders
83500	Metal grinders, polishers and tool sharpeners
85320	Electrical equipment assemblers

Table S3. Classification of welders in industries according to the International Standard Industrial Classification (ISIC) revision 2, SYNERGY, 1985-2010

ISIC Code	Description
Construction, plumbers and other building services	
5000	Construction
9100	Public administration and defence
4101	Education services
9310	Electric light and power
4102	Gas manufacture and distribution
4103	Steam and hot water supply
6320	Hotels, rooming houses, camps and other lodging places
8324	Engineering, architectural and technical services
8310	Real estate
Manufacture of machines, equipment, appliances	
3819	Manufacture of fabricated metal products except machinery and equipment
3813	Manufacture of structural metal products
3829	Machinery and equipment except electrical not elsewhere classified
3811	Manufacture of cutlery, hand tools and general hardware
3824	Manufacture of special industrial machinery and equipment except metal and wood working machinery
3800	Manufacture of fabricated Metal Products, Machinery and Equipment
3821	Manufacture of engines and turbines
3822	Manufacture of agricultural machinery and equipment
3833	Manufacture of electrical appliances and housewares
3831	Manufacture of electrical industrial machinery and apparatus
3812	Manufacture of furniture and fixtures primarily of metal
3823	Manufacture of metal and wood working machinery
3851	Manufacture of professional and scientific, and measuring and controlling equipment
3830	Manufacture of electrical machinery apparatus, appliances and supplies
3832	Manufacture of radio, television and communication equipment and apparatus
3839	Manufacture of electrical apparatus and supplies not elsewhere classified
3810	Manufacture of fabricated metal products, except machinery and equipment
3820	Manufacture of machinery except electrical
3825	Manufacture of office, computing and accounting machinery
Manufacture of motor vehicles, motor bikes, bikes	
3843	Manufacture of motor vehicles
3844	Manufacture of motorcycles and bicycles
Ship building and repairing	
3841	Ship building and repairing
Repair of transport equipment	
3842	Manufacture of railroad equipment
3845	Manufacture of aircraft
6100	Wholesale trade
7111	Railway transport
9513	Repair of motor vehicles and motorcycles

7112	Urban, suburban and inter-urban highway passenger transport
7110	Land transport
3849	Manufacture of transport equipment not elsewhere classified
7100	Transport and storage
7131	Air transport carriers
Others	
3710	Iron and steel basic industries
3699	Manufacture of non-metallic mineral products not elsewhere classified
1110	Agriculture and livestock production
3511	Manufacture of basic industrial chemicals except fertilizers
3530	Petroleum refineries
2100	Coal mining
3320	Manufacture of furniture and fixtures, except primarily of metal
3513	Manufacture of synthetic resins, plastic materials and man-made fibres except glass
3529	Manufacture of chemical products not elsewhere classified
3909	Manufacturing industries not elsewhere classified
2901	Stone quarrying, clay and sand pits
3720	Non-ferrous metal basic industries

Table S4. Sensitivity analyses for the association between welding and lung cancer in men, SYNERGY, 1985-2010

Occupations	Studies with population controls				Studies with hospital controls				Started working after 1979			
	No. Controls	No. Cases	OR3[a]	CI	No. Controls	No. Cases	OR3[a]	CI	No. Controls	No. Cases	OR3[a]	CI
Reference group[b]	13,100	10,366	1.00		2,931	3,196	1.00		551	229	1.00	
Welders	315	432	1.53	1.29, 1.82	112	162	1.10	0.84, 1.44	61	63	1.31	0.68, 2.58
Occasional welding tasks	1,584	1,651	1.17	1.08, 1.28	346	425	1.10	0.93, 1.30	115	101	1.51	0.94, 2.44

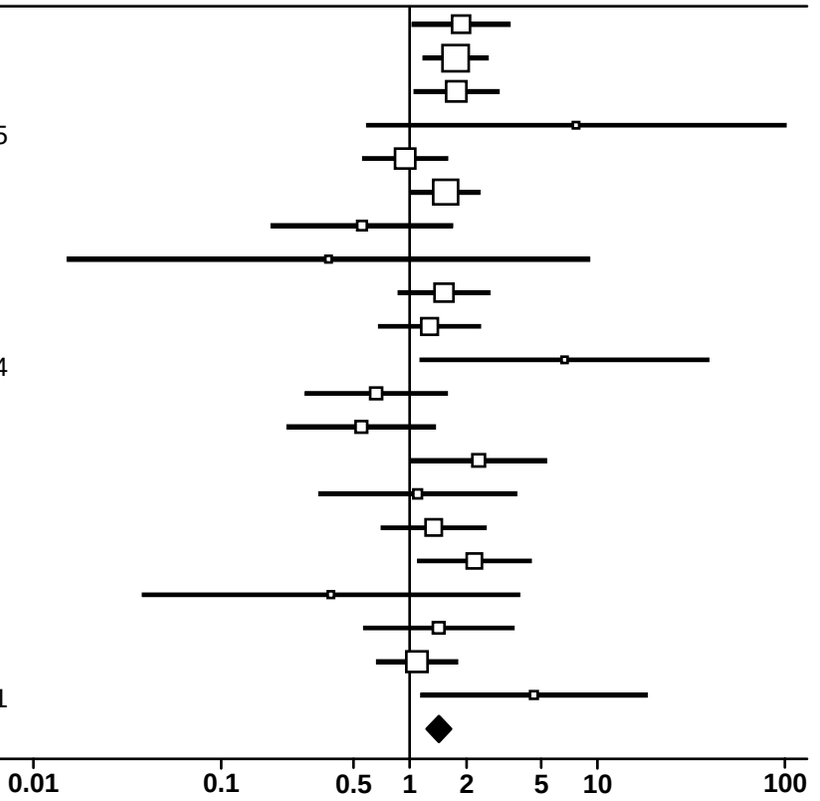
Abbreviations: CI, 95% confidence interval; OR, odds ratio.

[a] OR3 is adjusted for log(age), study centers, log(packyears+1), time-since-quitting smoking cigarettes (current smokers, ever other types of tobacco only, stopping smoking 2-7, 8-15, 16-25, 26+ years before interview/diagnosis, never smokers), and for ever working in a "List A" job.

[b] Defined as subjects, who had never worked in welding-related occupations.

A

Study	Welders Cases	Welders Controls	Never welding Cases	Never welding Controls	OR3	95%CI
HdA	42	18	637	697	1.87	1.03 , 3.42
AUT	101	49	2,099	2,268	1.75	1.14 , 2.61
TURIN/VENETO	43	34	822	1,104	1.77	1.05 , 2.98
ROME	4	1	265	242	7.65	0.59 , 99.75
EAGLE	40	39	1,312	1,449	0.94	0.56 , 1.59
ICARE	77	55	1,784	2,320	1.55	1.02 , 2.36
LUCA	7	7	258	250	0.56	0.18 , 1.70
PARIS	2	2	138	201	0.37	0.02 , 9.03
LUCAS	23	42	912	2,137	1.52	0.86 , 2.67
INCO-UK (LLP)	22	35	221	474	1.28	0.68 , 2.38
INCO-Czech Republic	8	4	200	261	6.63	1.13 , 38.84
INCO-Slovakia	15	14	243	199	0.66	0.28 , 1.58
INCO-Hungary	11	12	280	220	0.55	0.22 , 1.37
INCO-Poland	25	11	466	510	2.32	1.01 , 5.32
INCO-Romania	7	7	113	132	1.10	0.33 , 3.70
INCO-Russia	31	17	407	403	1.34	0.70 , 2.54
MONTREAL	29	16	595	776	2.21	1.10 , 4.41
TORONTO	1	5	175	348	0.38	0.04 , 3.87
QCANZ	15	15	162	344	1.43	0.57 , 3.58
CAPUA	51	38	651	603	1.09	0.66 , 1.80
HONG KONG	14	3	1,146	995	4.56	1.14 , 18.21
Overall (I^2=29.6%, *P*=0.10)					**1.42**	**1.23 , 1.66**



B

Study	Occasional welding Cases	Occasional welding Controls	Never welding Cases	Never welding Controls	OR3	95%CI
HdA	160	123	637	697	1.39	1.05 , 1.85
AUT	459	385	2,099	2,268	1.10	0.93 , 1.31
TURIN/VENETO	90	111	822	1,104	1.00	0.73 , 1.38
ROME	25	21	265	242	1.08	0.55 , 2.13
EAGLE	184	129	1,312	1,449	1.82	1.37 , 2.42
ICARE	382	374	1,784	2,320	1.18	0.97 , 1.43
LUCA	42	45	258	250	1.00	0.59 , 1.69
PARIS	21	16	138	201	1.64	0.56 , 4.82
LUCAS	83	130	912	2,137	1.46	1.07 , 1.99
MORGEN	6	10	35	98	2.10	0.55 , 8.00
INCO-UK (LLP)	38	64	221	474	1.26	0.79 , 2.02
INCO-Czech Republic	27	29	200	261	1.29	0.65 , 2.55
INCO-Slovakia	30	23	243	199	0.97	0.49 , 1.92
INCO-Hungary	22	18	280	220	1.07	0.51 , 2.25
INCO-Poland	60	53	466	510	1.21	0.78 , 1.87
INCO-Romania	21	13	113	132	1.69	0.73 , 3.92
INCO-Russia	83	83	407	403	0.83	0.58 , 1.19
MONTREAL	90	103	595	776	1.05	0.74 , 1.49
TORONTO	11	18	175	348	1.47	0.73 , 2.96
QCANZ	35	58	162	344	0.81	0.46 , 1.43
CAPUA	72	71	651	603	0.94	0.62 , 1.42
HONG KONG	42	53	1,146	995	0.77	0.47 , 1.27
Overall (I^2=20.9%, *P*=0.186)					**1.17**	**1.08 , 1.27**