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Title: Welding and the risk of head and neck cancer: the ICARE Study.

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Abstract:

Objective: to investigate the association between occupational exposure to welding and the risk of head and neck cancer in a large French population-based case-control study, the ICARE study. **Methods:** Analyses were restricted to men (2,703 controls and 1,588 cases of squamous-cell carcinoma of the oral cavity, oropharynx, hypopharynx and larynx. Welding activity and potential confounders were assessed by detailed questionnaires. Odds ratios (ORs) and confidence intervals (95%CI) were estimated by unconditional logistic regression, adjusted for age, area of residence, tobacco smoking, alcohol consumption, and occupational exposure to asbestos. **Results:** Welding was associated with an increased risk of head and neck cancer overall (OR = 1.31, 95%CI 1.03 to 1.67). The association was strongest for laryngeal cancer (OR = 1.66, 95%CI 1.15 to 2.38) and the risk increased with the cumulative duration (p-trend <0.01) and the weighted duration (p-trend <0.01) of welding. A cumulative duration and a weighted duration of welding of more than 10 years were also associated with a significantly increased risk of oral cancer (OR = 1.82, 95%CI 1.09 to 3.04; OR = 2.10, 95%CI 0.99 to 4.45, respectively). A long duration of arc welding was associated with laryngeal cancer, whereas a long duration of spot welding was associated with oral cancer. Welding was not associated with the risk of oropharyngeal and hypopharyngeal cancer.

Conclusion: Our findings suggest that welding and several welding-related tasks increase the risk of laryngeal cancer and to a lesser extent oral cancer.

Key terms: head and neck, epidemiology, occupational health, tumor, case-control study

Word Count: 3,497

Introduction

Welding fumes have been classified as carcinogenic to humans by the International Agency for Research on Cancer (IARC) because of sufficient evidence for lung cancer [1]. These fumes contain several chemicals which vary, depending on the metal to be welded, its coating, or the welding process [2,3]. For example, concentrations of nickel compounds and hexavalent chromium, recognized carcinogens, are much higher in stainless steel than in mild-steel. On the other hand, mild-steel welding generates higher mass concentrations of particulate matter than stainless steel welding. Welding also involves co-exposures to coatings of the welded metal, chemicals used to clean the metal before welding, and asbestos, as part of the protective equipment or from the working environment [1].

Few studies have examined the association between welding and the risk of head and neck cancer. Most cohort studies of welders did not report on these cancers, or included a small number of cases, and did not control for tobacco and alcohol consumption, the main risk factors of head and neck cancer [4]. Case-control studies on welding are more informative, as confounding by smoking and alcohol has routinely been accounted for. Positive associations between head and neck cancer and welding were reported in some [5–12], but not all case-control studies [13–18]. However, the majority of these studies were based on a small number of exposed cases and did not account for the confounding effect of asbestos exposure, a known occupational risk factor of laryngeal cancer to which welders are commonly exposed. In addition, very few studies have examined the risk of head and neck cancer according to the duration of welding [5], the use of a specific welding process [6] or the type of metal welded [7], although these are major determinants of exposure.

Previously, in a large French population-based case-control study, the ICARE study, we found increased risks of head and neck cancer among men [19] and women [20] who had been employed as ‘welders and flame-cutters’. However, the number of workers who perform welding may be ten times higher than the number of workers with the job title of welder [1,21].

Here, we aimed to investigate the association between head and neck cancer and welding as a job task, regardless of the job title. We examined several parameters of exposure and carefully took into account the main behavioural and occupational risk factors.

Methods

Study design

We used data from a French multicenter population-based case-control study, the ICARE study (Investigation of occupational and environmental **CA**uses of **RE**spiratory cancers study), conducted between 2001 and 2007 in ten geographical areas covered by a cancer registry. The detailed study design is available elsewhere [22]. Briefly, incident cases of head and neck cancer were collected from almost all healthcare establishments in each area in collaboration with cancer registries. Patients aged between 18 and 75 years, first diagnosed during the study period with a histologically confirmed primary cancer of the oral cavity, pharynx, or larynx fulfilled the eligibility criteria of the study. Controls were selected by incidence density sampling in the same geographical areas as the cases, with frequency-matching by gender and age. Additional stratification was performed to achieve an occupational class distribution in controls comparable to that of the general population of the same geographical areas. Participation rates were 80.6% for controls and 82.5% for cases [22].

The study was approved by the Institutional Review Board of the French National Institute of Health and Medical Research (IRB-Inserm, n° 01-036) and the French Data Protection Authority (CNIL n° 90120).

Data collection

Participants were interviewed face to face by trained interviewers with standardized questionnaires including sociodemographic characteristics, smoking and alcohol consumption history and detailed lifetime occupational history, covering all jobs held for at least one month. Participants who were severely ill or extremely tired (11% of cases/ 2% of controls) were interviewed either in person or through a next-of-kin with a shorter version of the questionnaire, which mainly covered information on tobacco and alcohol consumption and occupational history. The international Standard Classification of Occupations (ISCO) and the French Nomenclature of Activities were used by trained coders to code occupations

and branches of the industry, independently of the case-control status of the participants [23,24].

A job-specific questionnaire on welding, brazing and flame cutting was given to participants for whom at least 5% of their working time was devoted to this task.

Assessment of welding activity

Welding was defined as having at least one job period as 'welder and flame-cutter' (coded 872 in ISCO code) and/or having declared a welding or flame-cutting activity in the general questionnaire that occupied at least 5% of the working time in at least one job of the occupational lifetime. Other participants were included in the 'no welding' category. Participants were interviewed with the specific questionnaire on welding, which contained detailed questions about the welding processes, the type of metals welded, the treatments (mechanical or chemical) used to clean the surface before welding and the duration and associated frequency of welding (as a percentage of working time) for each job period.

Assessment of other occupational exposures

Occupational exposure to asbestos was assessed through a specific job-exposure matrix accounting for exposure generated by the occupational tasks and the occupational environment [25]. Information on exposure to strong inorganic acids was obtained for each job from specific questions in the questionnaire.

Study sample

The present study was restricted to men, as only ten women (4 cases/6 controls) were welders [20] and seven others (only controls) were not but reported a welding activity of more than 5% of their working time. The study was also restricted to squamous cell carcinomas of the following cancer sites, according to the codes of the International Classification of Diseases for Oncology, third edition (ICD-O-3): oral cavity (C00.3-9; C02.0-3; C03.0-1; C03.9, C04.0-1; C04.8-9; C05.0; C06.0-2; C06.8-9), oropharynx (C01.9; C02.4; C05.1-2; C09.0-1; C09.8-9; C10.0-4; C10.8-9), hypopharynx (C12.9; C13.0-2; C13.8; C13.9), oral cavity or pharynx not otherwise specified or overlapping (C02.8, C02.9, C05.8, C05.9, C14.0,

C14.2, C14.8), and larynx (C32.0-3; C32.8-9). Participants with missing data concerning welding were excluded (269 cases and 77 controls).

Overall, 1,588 male cases of head and neck cancer (301 with oral cancer, 472 with oropharyngeal cancer, 316 with hypopharyngeal cancer, 107 with oral or pharyngeal cancer not otherwise specified or overlapping and 392 with laryngeal cancer) and 2,703 male controls were included in the study.

Statistical analysis

Odds ratios (ORs) and confidence intervals (95%CI) were estimated using multivariable unconditional logistic regression, modelling the association between welding and the overall risk of head and neck cancer and by specific anatomical sites (oral cavity, oropharynx, hypopharynx, and larynx). Analyses were adjusted for age at interview, area of residence, alcohol consumption (glass/day), smoking status (never, former: time since stopping smoking > 2 years at the time of the interview, current), daily amount of tobacco consumption (gram/day), duration of tobacco smoking (years), and a cumulative index of occupational exposure to asbestos. To allow for non-linear associations, continuous variables were included in the models as restricted cubic splines, with three knots for age and alcohol consumption and four knots for amount and duration of tobacco smoking and asbestos exposure. For laryngeal cancer, additional adjustment for self-reported occupational exposure to strong inorganic acids (sulfuric and/or hydrochloric acids) was also performed.

No welding was the reference category for all analyses. We examined the associations between the risk of head and neck cancer and the total cumulative duration of welding. In order to better reflect the real exposure, we also calculated a weighted duration over all jobs as follows:

$$WD = \sum (D_i \times F_i)$$

Where D_i is the duration of the job i and F_i the frequency of welding in the job i , expressed as a proportion of the working time. These continuous exposure variables were categorized according to approximate percentiles on exposed controls' distributions (median for duration of welding; quartiles for weighted duration of welding). Tests for trend were performed using the median value for each category as an ordinal variable.

Finally, we estimated the risk of head and neck cancer according to the most common welding processes, the type of metals welded and the use of chemical or mechanical treatments to clean the surface before welding. All analyses were performed using SAS (version 9.4; SAS Institute, Cary, North Carolina).

Results

Overall, 242 cases (16%) and 299 controls (11%) had welded in their working life. Among them, 32% (100 cases and 71 controls) had ever worked as “welders and flame cutters” (ISCO code 8.72) and 68% (142 cases and 228 controls) had never been employed in this occupational group, but had performed welding in other jobs. These other jobs were mainly sheet-metal workers (17%, ISCO code 8.73), plumbers and pipe fitters (16%, ISCO code 8.71) machinery fitters, machine assemblers and precision instrument makers (18%, ISCO code 8.4) and blacksmiths, toolmakers and machine-tool operators (11%, ISCO code 8.3).

The associations between welding and the risk of head and neck cancer are presented in **Table 1**. Welding was associated with an increased risk of head and neck cancer (OR = 1.31, 95%CI 1.03 to 1.67) and the risk increased with the cumulative duration (p-trend=0.01) and the weighted duration (p-trend=0.05) of welding. The association was strongest for laryngeal cancer (OR = 1.66, 95%CI 1.15 to 2.38), particularly for welding more than 10 years, either considering the cumulative duration (OR=1.87, 95%CI 1.20 to 2.94) or the weighted duration of welding (OR = 2.42, 95%CI 1.25 to 4.69), with significant increasing trends for both metrics (p <0.01). Welding was not associated with oral cancer but an increased risk was found for the longest cumulative duration (OR= 1.82; 95% 1.09 to 3.04) and weighted duration (OR= 2.10, 95% 0.99 to 4.45), with borderline significant trends (p=0.07, p=0.05, respectively). We found no association between welding and the risk of oropharyngeal or hypopharyngeal cancer.

Table 1. Risk of head and neck cancer associated with welding.

	Controls		Cases		Oral cavity			Oropharynx			Hypopharynx			Larynx		
	n	n	OR [*]	95%CI	n	OR [*]	95%CI	n	OR [*]	95%CI	n	OR [*]	95%CI	n	OR [*]	95%CI
No welding [†]	2316	1267	1	Ref	244	1	Ref	380	1	Ref	243	1	Ref	315	1	Ref
Welding	299	242	1.31	1.03 to 1.67	43	1.29	0.85 to 1.97	68	0.96	0.67 to 1.38	51	1.37	0.91 to 2.06	62	1.66	1.15 to 2.38
<i>Cumulative duration of welding (years)</i>																
≤ 10	136	90	1.07	0.75 to 1.53	13	0.75	0.38 to 1.49	29	0.81	0.47 to 1.37	20	1.30	0.72 to 2.36	22	1.39	0.81 to 2.39
> 10	163	150	1.50	1.10 to 2.04	30	1.82	1.09 to 3.04	39	1.04	0.70 to 1.75	29	1.29	0.76 to 2.18	40	1.87	1.20 to 2.94
p-trend			0.01			0.07			0.91			0.25			<0.01	
<i>Weighted duration of welding (years)</i>																
≤ 1	65	31	1.03	0.61 to 1.75	5	0.87	0.31 to 2.46	10	0.86	0.39 to 1.90	7	1.21	0.49 to 2.99	6	1.06	0.43 to 2.64
[1 to 5 [88	60	0.95	0.61 to 1.48	10	0.86	0.39 to 1.90	21	0.87	0.46 to 1.64	10	0.69	0.29 to 1.63	13	1.00	0.50 to 1.99
[5 to 10]	25	28	1.63	0.78 to 3.40	7	2.50	0.82 to 7.66	6	1.04	0.35 to 3.15	5	1.49	0.45 to 4.95	8	2.53	0.98 to 6.51
> 10	47	65	1.61	0.99 to 2.62	13	2.10	0.99 to 4.45	14	0.90	0.44 to 1.82	16	1.58	0.78 to 3.23	19	2.42	1.25 to 4.69
p-trend			0.05			0.05			0.67			0.30			<0.01	

Abbreviations: y = years, OR = odds-ratio, CI = confidence interval, Ca: cases, Co: controls

*OR adjusted for age at interview, area of residence, alcohol consumption, smoking status, frequency and duration of smoking, and exposure to asbestos.

†Reference category contains participants who had never welded and those who had welded less than 5% of their working time in all their jobs involving welding.

We explored the role of the most common welding processes and the corresponding weighted durations (**Table 2**). We observed a significant increased risk of head and neck cancer related to having ever performed arc welding (OR=1.36, 95%CI 1.02 to 1.81) and a borderline significant OR of 1.58 linked to a long-term weighted duration using this process. In analyses by subsite, an increased risk of oral cancer emerged in workers with the longest weighted duration of spot welding (OR=3.47, 95%CI 1.27 to 9.48). An increased risk of laryngeal cancer appeared in workers who had ever gas welded (OR=1.54, 95%CI 1.01 to 2.34) and in those with the longest weighted duration of arc welding (OR=2.42, 95%CI 1.27 to 4.60). No other significant association was found. It should be noted that analyses by subsite according to weighted duration were based on a small number of exposed cases.

Table 2. Risk of head and neck cancer associated with the ever use and the weighted duration of a welding process

	Controls		Cases		Oral cavity			Oropharynx			Hypopharynx			Larynx		
	n	n	OR [†]	95%CI	n	OR [†]	95%CI	n	OR [†]	95%CI	n	OR [†]	95%CI	n	OR [†]	95%CI
No welding [†]	2316	1267	1	Ref	244	1	Ref	380	1	Ref	243	1	Ref	315	1	Ref
<i>Ever use of a welding process[‡]</i>																
Soldering	117	89	1.22	0.84 to 1.77	16	1.26	0.66 to 2.38	21	0.83	0.47 to 1.47	19	1.20	0.64 to 2.27	26	1.54	0.90 to 2.62
Brazing	95	53	0.95	0.61 to 1.79	11	0.88	0.42 to 1.88	16	0.79	0.41 to 1.51	10	0.79	0.35 to 1.76	13	1.03	0.52 to 2.04
Gas welding	219	173	1.26	0.95 to 1.67	35	1.40	0.87 to 2.25	51	1.01	0.67 to 1.52	30	1.00	0.61 to 1.66	45	1.54	1.01 to 2.34
Arc welding	199	169	1.36	1.02 to 1.81	34	1.58	0.97 to 2.56	49	1.15	0.76 to 1.77	31	1.28	0.78 to 2.12	40	1.53	0.98 to 2.37
Spot welding	94	71	1.27	0.84 to 1.92	15	1.63	0.82 to 3.24	17	0.77	0.41 to 1.47	11	0.90	0.42 to 1.92	19	1.48	0.80 to 2.72
<i>Weighted duration by welding process (years)</i>																
Soldering																
] 0 to 0.30]	33	13	0.60	0.27 to 1.32	2	0.71	0.16 to 3.22	4	0.51	0.15 to 1.73	2	0.34	0.07 to 1.74	4	0.92	0.28 to 3.00
> 0.30	34	28	1.06	0.54 to 2.06	5	1.04	0.34 to 3.14	6	0.77	0.29 to 2.07	8	1.07	0.36 to 3.12	6	1.12	0.42 to 3.01
Brazing																
] 0 to 0.61]	27	9	0.57	0.22 to 1.45	1	0.28	0.03 to 2.33	4	0.59	0.17 to 2.12	1	0.19	0.02 to 1.60	2	0.50	0.10 to 2.43
> 0.61	26	16	1.15	0.50 to 2.67	3	1.14	0.30 to 4.36	6	1.08	0.35 to 3.28	5	1.53	0.41 to 5.78	2	0.52	0.10 to 2.59
Gas welding																
] 0 to 0.90]	72	39	0.97	0.58 to 1.60	5	0.49	0.16 to 1.44	12	0.70	0.32 to 1.51	8	0.79	0.32 to 1.95	13	1.65	0.82 to 3.33
> 0.90	67	65	1.41	0.89 to 2.23	13	1.89	0.91 to 3.88	16	0.87	0.44 to 1.73	14	1.17	0.55 to 2.50	16	1.46	0.74 to 2.91
Arc welding																
] 0 to 1.70]	57	38	1.31	0.76 to 2.24	8	1.14	0.46 to 2.85	4	1.50	0.71 to 3.17	7	0.75	0.26 to 2.12	8	1.33	0.56 to 3.13
> 1.70	56	69	1.58	0.99 to 2.51	8	1.35	0.56 to 3.25	7	1.05	0.55 to 2.03	16	1.80	0.89 to 3.64	20	2.42	1.27 to 4.60
Spot welding																
] 0 to 0.58]	27	20	1.14	0.53 to 2.48	2	0.45	0.09 to 2.33	6	0.93	0.29 to 2.91	4	0.71	0.19 to 2.67	4	1.04	0.30 to 3.68
> 0.58	27	21	1.32	0.65 to 2.70	7	3.47	1.27 to 9.48	3	0.42	0.11 to 1.64	5	1.54	0.50 to 4.69	4	1.33	0.42 to 4.22

Abbreviations: OR = odds-ratio, CI = confidence interval

[†]OR adjusted for age at interview, area of residence, alcohol consumption, smoking status, frequency and duration of smoking, and exposure to asbestos

[‡]Reference category contains participants who had never welded and those who had welded less than 5% of their working time in all their jobs involving welding.

[‡]Welding processes were not mutually exclusive.

We also investigated the role of the type of metal welded (**Table 3**). Having ever welded iron was associated with an increased risk of laryngeal cancer (OR=1.83, 95%CI 1.01 to 3.34). There was no other association between the ever use of a specific metal and the risk of head and neck cancer overall and by subsite, although for most metals the number of exposed cases by subsite was small.

Table 3. Risk of head and neck cancers associated with the type of welded metal

	Controls		Cases		Oral cavity			Oropharynx			Hypopharynx			Larynx		
	n	n	OR*	95%CI	n	OR*	95%CI	n	OR*	95%CI	n	OR*	95%CI	n	OR*	95%CI
No welding†	2316	1267	1	Ref	244	1	Ref	380	1	Ref	243	1	Ref	315	1	Ref
<i>Ever welded metal</i>																
Aluminium	22	24	1.36	0.63 to 2.95	5	2.86	0.83 to 9.88	9	1.55	0.57 to 4.22	3	0.79	0.18 to 3.44	6	1.71	0.55 to 5.28
Lead	19	21	1.20	0.53 to 2.73	5	1.39	0.43 to 4.52	5	0.79	0.23 to 2.70	4	1.28	0.32 to 5.17	5	1.10	0.33 to 3.70
Cast iron	22	20	0.93	0.42 to 2.06	2	0.59	0.12 to 2.90	7	0.85	0.29 to 2.49	5	1.10	0.32 to 3.76	5	0.95	0.29 to 3.04
Copper	32	48	1.74	0.97 to 3.15	8	1.63	0.63 to 4.23	15	1.57	0.72 to 3.42	9	1.01	0.36 to 2.80	11	2.03	0.89 to 4.63
Galvanized metal	39	41	1.00	0.55 to 1.84	4	0.72	0.22 to 2.42	16	1.22	0.57 to 2.61	8	0.82	0.30 to 2.23	8	1.03	0.40 to 2.64
Stainless steel	31	38	1.58	0.84 to 2.99	5	1.47	0.46 to 4.73	14	1.71	0.76 to 3.86	7	1.42	0.50 to 4.03	8	1.76	0.68 to 4.56
Mild steel	86	63	0.98	0.64 to 1.52	10	0.88	0.40 to 1.94	20	0.98	0.53 to 1.80	11	0.69	0.32 to 1.50	17	1.29	0.68 to 2.47
Iron	79	78	1.39	0.91 to 2.11	10	0.98	0.43 to 2.25	22	1.06	0.58 to 1.93	20	1.51	0.79 to 2.91	21	1.83	1.01 to 3.34

Abbreviations: OR = odds-ratio, CI = confidence interval

*OR adjusted for age at interview, area of residence, alcohol consumption, smoking status, frequency and duration of smoking, and exposure to asbestos

†Reference category contains participants who had never welded and those who had welded less than 5% of their working time in all their jobs involving welding.

We examined the risk of head and neck cancer according to the treatment used to clean the surface before welding (**Table 4**). Cleaning exclusively with a mechanical treatment was associated with a higher risk of head and neck cancer (OR=1.42, 95%CI 1.06 to 1.92) and of laryngeal cancer (OR = 1.66, 95%CI 1.11; 2.50). The ever use of chemical treatments was not associated with the risk of head and neck cancer. However, when chemicals were analyzed separately, having ever used acid was associated with an increased risk of head and neck cancer (OR = 2.69, 95%CI 1.19; 6.09), particularly oral (OR = 4.42, 95%CI 1.53; 12.72) and laryngeal cancer (OR = 4.53, 95%CI 1.73; 11.89). No association was found for the other chemical treatments.

Table 4. Risk of head and neck cancer associated with the type of treatment used before welding

	Controls		Cases		Oral cavity			Oropharynx			Hypopharynx			Larynx		
	n	n	OR [†]	95%CI	n	OR [†]	95%CI	n	OR [†]	95%CI	n	OR [†]	95%CI	n	OR [†]	95%CI
No welding	2316	1267	1	Ref	244	1	Ref	380	1	Ref	243	1	Ref	315	1	Ref
Exclusive use of mechanical treatments (never use of chemicals)	176	160	1.42	1.06 to 1.92	30	1.46	0.92 to 2.32	43	1.22	0.81 to 1.83	33	1.34	0.85 to 2.12	42	1.66	1.11 to 2.50
Ever used of chemicals	122	82	1.15	0.79 to 1.67	13	1.01	0.53 to 1.93	25	1.09	0.65 to 1.81	18	1.20	0.67 to 2.14	20	1.22	0.70 to 2.10
<i>Type of chemicals</i>																
Paint stripper	32	24	1.75	0.83 to 3.69	4	1.80	0.55 to 5.89	6	1.32	0.47 to 3.71	4	1.43	0.43 to 4.71	7	2.13	0.80 to 5.64
Trichloroethylene	56	46	1.39	0.82 to 2.35	8	1.31	0.57 to 3.04	13	1.25	0.62 to 2.54	10	1.42	0.65 to 3.12	11	1.43	0.68 to 3.02
Gasoline	28	18	0.94	0.44 to 2.03	3	0.81	0.22 to 2.99	6	0.99	0.36 to 2.74	2	0.52	0.11 to 2.39	6	1.34	0.49 to 3.66
White spirits	28	25	1.67	0.82 to 3.40	6	2.34	0.85 to 6.47	6	1.22	0.45 to 3.33	5	1.61	0.54 to 4.78	5	1.45	0.50 to 4.21
Acid	16	26	2.69	1.19 to 6.09	7	4.42	1.53 to 12.72	3	0.91	0.24 to 3.52	4	1.92	0.55 to 6.66	10	4.53	1.73 to 11.89

Abbreviations: OR = odds-ratio, CI = confidence interval

[†]OR adjusted for age at interview, area of residence, alcohol consumption, smoking status, frequency and duration of smoking, and exposure to asbestos

[†]Reference category contains participants who had never welded and those who had welded less than 5% of their working time in all their jobs involving welding.

As only seven participants (all cases) had data reported from next-of-kin, only marginal changes were found in sensitivity analyses removing those participants (data not shown). Finally, we investigated the role of welding in laryngeal cancer risk by additionally accounting for occupational exposure to strong inorganic acids. No substantial change was found in risk estimates (**Supplementary Table S1**). An increased risk of laryngeal cancer persisted in association with welding (OR=1.67, 95%CI 1.16 to 2.41), and the risk increased with the cumulative duration (p-trend <0.01) and the weighted duration of exposure (p-trend <0.01). A long-term duration of arc welding remained associated with an elevated risk of laryngeal cancer (OR=2.41, 95%CI 1.27 to 4.59).

Discussion

This study aimed to investigate the association between welding and the risk of head and neck cancer in men.

Here, welding was associated with an increased risk of head and neck cancer. The association was strongest for laryngeal cancer, with significant trends with duration. The increased risk of laryngeal cancer was particularly related to arc welding, welding iron, using exclusively mechanical treatments to clean metals before welding and cleaning with acid. Increased risk of oral cancer was associated with a long duration of welding, with the use of acid before welding and with spot welding. Welding was not associated with the occurrence of oropharyngeal and hypopharyngeal cancer.

Findings have been sparse in cohort studies that investigated head and neck cancer by anatomical site. Only one cohort study considered oral and pharyngeal cancer together and reported a SIR of 1.60 of borderline significance in welders (18 exposed cases). Several cohort studies have reported an elevated risk of laryngeal cancer for welders overall [26,27] or specifically for gas welders [28], whereas others did not find any association [29–32]. These studies did not consider the confounding effects of smoking, alcohol consumption or occupational exposure to asbestos and strong inorganic acids, all known risk factors for laryngeal cancer.

Most case-control studies used the job title of “welder” as a proxy for exposure to welding fumes [8–13,15–19], whereas a few focused on exposure to welding fumes [5–7]. Some of the studies using the job title of “welder” reported elevated ORs for oral cancer [8], oral and pharyngeal cancers combined [10], oropharyngeal and hypopharyngeal combined [12], hypopharyngeal and laryngeal cancers combined [11] and laryngeal cancer [9,12], whereas others did not find any increased risk [13–18]. The largest one, a pooled analysis of 12 case-control studies (including 25% of subjects from the ICARE study), based on 475 welders and flame-cutters (256 cases/219 controls), reported higher risks of head and neck

cancer (OR= 1.51, 95%CI 1.20 to 1.90), oropharyngeal and hypopharyngeal cancer combined (OR=1.42, 95%CI 1.01 to 1.99) and laryngeal cancer (OR= 1.52, 95%CI 1.14 to 2.02) [12]. An increased risk of head and neck cancer (OR=1.9, 95%CI 1.3 to 2.3), including oral (OR=1.9, 95%CI 1.1 to 3.3), hypopharyngeal (OR=2.1, 95%CI 1.2 to 3.6) and laryngeal cancer (OR=2.4, 95%CI 1.5 to 4.0) was also previously reported in male welders and flame cutters in the ICARE study [19]. In the present study risk estimates associated with welding were weaker, because men employed as welders and flame-cutters had on average a longer weighted duration of welding (12 years \pm 12) than men who reported welding in other jobs (5 years \pm 7). In addition, adjustment for asbestos exposure in our study led to a decrease in ORs.

Three case-control studies reported on the association between welding fumes and head and neck cancer. In a Swedish one, no increased risk of oral cancer was found associated with exposure to welding fumes, whereas borderline significantly elevated ORs were reported for pharyngeal and laryngeal cancers [5]. A borderline significantly OR was also reported for laryngeal cancer in a study from Denmark [7]. Inversely, no increased risk of hypopharyngeal and laryngeal cancer was found to be associated with welding fumes in a European multicenter study [6].

In summary, the available evidence is the strongest for laryngeal cancer, results are inconsistent for oral and hypopharyngeal cancer, and no association has been reported for oropharyngeal cancer. All case-control studies controlled for possible confounding effects of tobacco and alcohol consumption, but our study is the first to also adjust for occupational exposure to asbestos and to strong inorganic acids.

To date, only one study examined ever exposure to arc and gas welding fumes and reported ORs below 1 for laryngeal cancer. In this study, tobacco and alcohol consumption were controlled for in the analyses and asbestos and strong inorganic acids exposures were not associated with laryngeal cancer [6]. Here, we found an increased risk of laryngeal

cancer associated with the longest weighted durations of arc welding with an indication of a dose-response relationship. The evidence was less clear for gas welding as there was no suggestion of an increasing trend in risk with weighted duration. Our study is the first to provide such detailed results.

With respect to the welded metals, a previous study reported a non-significant OR of 1.30 for laryngeal cancer associated with stainless steel welding. This result concurs with our findings, although exposure to asbestos was not taken into account [7]. We found a moderate increased risk of laryngeal cancer linked to having welded iron. This is the first investigation of this association. Further studies focusing on the role of metals used in welding in the occurrence of head and neck cancer are needed.

Using acid to prepare metal for welding was associated with an increased risk of laryngeal cancer. We did not have information on the type of acid. Exposure to strong inorganic acid mists is a known risk factor for laryngeal cancer [33]. We also observed an increased risk of oral cancer in these workers.

Cleaning exclusively with mechanical treatments was associated with a higher risk of laryngeal cancer. Mechanical treatments including brushing, grinding, sand blasting or shot blasting are indicated when coatings have to be removed from the metals. Welders who used mechanical treatments are likely to have been exposed to higher levels of metal dust, paint dust and rust particles. The role of the treatment used to clean metals before welding has never been examined in the occurrence of head and neck cancer before.

The use of respiratory protection equipment may reduce the level of exposure to welding fumes but was reported by only 7% (11 controls/7 cases) of the exposed participants. Respirator use was reported as plain text in an open question and was not systematically collected, which limited further investigation of this topic.

The main limitation of our study was our inability to isolate the role of specific welding processes, metals and methods of treating the surface to be welded, because few

participants used an exclusive welding process, metal or treatment before welding. In addition, sub-group analyses by cancer site were generally based on a small number of cases. Detailed welding activity was self-reported that could result in inflated risk estimates due to differential recall bias. However, this is likely not a major limitation here. Welding is not commonly perceived to be associated with head and neck cancer and the study was presented to participants as a study investigating 'health and environment'. Therefore, any exposure misclassification may rather be non-differential, which may have bias our estimates towards the null and underestimate the true effect of welding.

Information on human papillomavirus infection (HPV), a risk factor for oropharyngeal cancer, was not available. However, HPV infection is unlikely to be associated with welding. The prevalence of head and neck cancer caused by HPV infection was low in men during the study period [34], decreasing the probability of a major confounding bias in our analyses.

In addition to the many aspects of welding activity that we could investigate through our detailed questionnaire, several strengths reinforce the robustness of our study. The participation rate was good for cases and controls. Cases included in the ICARE study were incident cases with a distribution by age and cancer site similar to that observed in France [35]. Controls were randomly selected, conditional on age, from the same regions as the cases through incidence density sampling. A large number of participants were included in the study, providing sufficient statistical power to detect moderate associations and to investigate head and neck cancers overall and by anatomical subsite. Besides welders, we identified workers who used the technique in other jobs. Moreover, we took precautions to minimize confounding bias by considering major confounders, including tobacco and alcohol consumption and occupational exposure to asbestos and acid.

The evidence for the carcinogenicity of welding fumes for head and neck cancer is limited, mainly because of an insufficient number of studies investigating the association and inconsistent findings in epidemiological studies. No specific biological mechanism has yet

been identified. Inhalation is the main route of exposure to welding fumes, directly exposing the epithelium of the upper respiratory tract to many induced particles. There is strong evidence that welding fumes induce inflammation and immunosuppression [1]. These mechanisms, involved in lung carcinogenicity of welding fumes, could be relevant for other parts of the respiratory tract.

Conclusion:

This study provides evidence that welding and several welding-related tasks increase the risk of laryngeal cancer, and to a lesser extent oral cancer.

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Contributors:

DL and CB designed the current study, conducted the analyses and drafted the manuscript; MM, AA, JD, LR and GM contributed to the statistical analysis and interpretation of the results. JF was involved in exposure assessment. AVG contributed to data collection and quality control. DL and IS are the principal investigators of the ICARE study, conceived this study and coordinated the original collection of the data. All the authors critically reviewed and revised the manuscript, and gave their approval for its final version.

Competing interest

The authors declare no conflict of interest.

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What this paper adds?

What is already known about this subject?

- Evidence about the role of welding on head and neck cancer risk is inconclusive

What are the new findings?

- We found that welding increased the risk of laryngeal cancer.
- Long-term welding increases the risk of oral cancer
- Using acid to clean metal before welding was associated with an increased risk of oral and laryngeal cancer.

How might this impact on policy or clinical practice in the foreseeable future?

- If replicated in future studies, these findings can impact on work practices and workplace preventive policies, as well as on compensation of occupational diseases.