Risk factors for salivary gland cancers in France: Results from a case-control study, the ICARE study

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Abstract

Objectives

Epidemiological studies on the risk factors for salivary gland cancers (SGC) are rare, concern a small sample size, and show inconsistent results. The aim of the present work was to analyze several risk factors for SGC, using the data from the ICARE study, a multicenter, population-based case-control study.

Materials and methods

Data from 73 SGC cases and 3555 controls were collected using a standardized questionnaire on lifestyle habits, personal and family medical history, and lifetime occupational history. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using unconditional logistic regressions.

Results

Tobacco use and alcohol consumption were not associated with the risk of SGC. A history of head and neck cancer or that of cervicofacial radiotherapy was associated with a higher risk of SGC (OR = 17.06, 95% CI: 4.34–67.05, and OR = 31.74, 2.48–405.25, respectively). Significantly increased risks were observed for some occupations: waiter (OR = 2.94, 1.11–7.78), charworker (OR = 3.02, 1.38–6.60), electrical and electronic equipment assembler (OR = 7.16, 2.02–25.38), plumber (OR = 3.95, 1.33–11.67), electric arc welder (OR = 6.15, 1.76–21.48), sheet-metal worker (OR = 2.89, 1.01–8.32), building painter (OR = 3.42, 1.01–11.49), and material handling equipment operator (OR = 5.05, 1.71–14.84). Results for industries were consistent with those observed for occupations.

Conclusion

Our results showed that a history of head and neck cancer, cervicofacial radiotherapy, and several occupations and industries, were associated with an increased risk of SGC. Further studies with larger sample sizes are indicated to confirm our results.

Keywords: Salivary gland neoplasms; Head and neck cancers; Occupations; Industry; Epidemiologic studies; Risk factors; Life style

Abbreviations: SGC, salivary gland cancers; HNC, head and neck cancers; BMI, body mass index; ICARE, Investigation of occupational and environmental causes of respiratory cancers; JEM, job-exposure matrices; ISCO, International Standard Classification of Occupations; NAF, French Nomenclature of Activities; CEI, cumulative exposure index; OR, odds ratio; CI, confidence interval

Introduction

The major salivary glands occur in three pairs (the parotid, submandibular, and the sublingual glands), while the minor salivary glands occur as several hundred structures scattered within the mucous membranes of the mouth, oropharynx, larynx, nose, and the paranasal sinuses. In France, the cancers of the major salivary glands are rare, with an estimated incidence of 0.7/100,000 person-years in men and 0.5/100,000 person-years in women [1], and account for 1.9% and 8.6% of head and neck cancers (HNC) in men and in women, respectively [2]. The incidence rates of the cancers of the minor salivary glands have not been estimated.

The etiology of salivary gland cancers (SGC) is not well known. Unlike most HNC, the SGC are not generally considered to be related to tobacco smoking and alcohol drinking, although some studies showed an increased risk in smokers [3–5] and drinkers [4,6]. The only established risk factor is the exposure to ionizing radiation, particularly during radiotherapy [4,6–10] and during dental or cervicofacial radiological examinations [4,9,11]. The role of several occupational exposures has been suggested [4,6,10–20]. Other suspected risk factors include dietary factors [11,13,21–23], a high body mass index (BMI) [13,23], the use of mobile telephones [24–29], a family history of cancer [13], and certain viral infections [30–35].

Epidemiological studies on the risk factors for SGC are rare, concern a low number of cases, and show inconsistent results. Moreover, most studies have focused on the major SGC (occasionally restricted to parotid gland neoplasms), and have sometimes included both benign and malignant tumors, despite the fact that certain types of benign tumors (e.g., Warthin's tumor) are strongly related to tobacco smoking [5,12,36]. Only two studies have included both major and minor SGC [3,37].

In this context, the objective of the present work was to study the role of several non-occupational and occupational risk factors in the occurrence of SGC, based on the data from the ICARE (**I**nvestigation of occupational and environmental **CA**uses of **RE**spiratory cancers) study.

Materiel and methods

Study population

The details of the study design have been reported previously [38]. Briefly, the ICARE study is a multicenter, population-based case-control study, which was conducted between 2001 and 2007 in 10 French *départements* (geographic and administrative areas), covered by general cancer registries. The study included 2926 lung cancer cases, 2415 HNC cases, and 3555 control subjects. Incident cases were identified in collaboration with the French cancer registries. All cases were histologically confirmed primary tumors occurring in patients aged 18 to 75 years at diagnosis. Controls were selected by list-assisted random digit dialing sampling and an incidence density sampling method, from the general population of the *départements* included in the study. In each *département*, controls were frequency-matched to all cases (lung cancer and HNC) by sex and age. Additional stratification was used to achieve a socioeconomic status distribution among the controls comparable to that of the general population of each *département*.

Study sample

The present analysis was restricted to SGCs and the controls of the ICARE study. Patients with primitive cancers of the major salivary glands (parotid, submandibular, and sublingual glands) (topographical codes C07-C08 and all morphological codes of the International Classification of Diseases for Oncology, ICD-O-3) or with primitive cancers of the minor salivary glands (topographical codes C00-C14, C30.0, C31, and C32 and morphological codes 8147, 8200, 8290, 8310, 8430, 8440, 8450, 8480, 8500, 8525, 8550, 8562, 8941, 8980, and 8982 of the ICD-O-3) [39] were identified. Among the 116 eligible patients, 22 could not be reached, 7 were deceased, and 3 were too sick to be interviewed. Of the 84 patients who were contacted, 11 refused to participate. Among the 4673 eligible control subjects, 230 could not be reached, 5 were deceased, and 27 were too sick to participate. Of the 4411 subjects who were contacted, 856 refused to participate. Finally, 73 patients and 3555 controls were included in the analysis (participation rates: 86.9% and 80.6%, respectively). Eligible subjects who were contacted but who refused to participate had a sex and age distribution similar to that of the included subjects.

Each subject gave written informed consent. The study was approved by the Institutional Review Board of the French National Institute of Health and Medical Research (IRB-Inserm, No. 01-036), and by the French Data Protection Authority (CNIL No. 90120).

Data collection

Using a standardized questionnaire, subjects were interviewed face-to-face by trained interviewers to collect information on sociodemographic characteristics, anthropometric characteristics, personal and family history of cancer, lifetime tobacco and alcohol consumption, and lifetime occupational history, with a detailed description of each job held for at least one month during the working life.

Several parameters were available for both tobacco smoking and alcohol drinking: status (never, current, former), quantity, duration, and lifetime cumulative quantity (pack-years/glass-years). Ever smokers were defined as subjects who had smoked at least 100 cigarettes in their lifetime or those who had smoked at least one pipe, cigar, or cigarillo per week for at least one year. Ever drinkers were defined as subjects who had consumed at least one drink per month for at least one year. Former smokers and former drinkers were defined as subjects who had not smoked or consumed alcohol for at least two years before the interview for the controls and before the diagnosis for the cases. The quantity of tobacco smoked (g/day) and alcohol consumed (standard glasses/day) were calculated by using the average lifetime daily consumption of all types of products consumed.

BMI was computed as weight (kg) divided by height squared (m^2) and categorized into four classes: <18.5 (underweight), 18.5–24.9 (normal weight), 25.0–29.9 (overweight), and >30 (obesity).

Using data from the occupational history questionnaire, trained coders blinded to case or control status coded industries according to the French Nomenclature of Activities (NAF, 1999) [40] and coded occupations according to the International Standard Classification of Occupations (ISCO, 1968) [41].

The assessment of occupational exposures (to chlorinated, oxygenated and petroleum solvents, asbestos, silica, cement, refractory ceramic fibers, and mineral wool) was made by using job-exposure matrices (JEMs), developed by the French Public Health Agency [42].

For each combination of ISCO and NAF codes, the JEMs assigned three exposure indices: probability of exposure (percentage of exposed workers), intensity of exposure, and frequency of exposure (percentage of the working time during which the subject was exposed) [42]. For each subject, we derived from his or her entire occupational history the exposure status, the cumulative duration of exposure, and the cumulative exposure index (CEI). Regarding the exposure status, a subject was considered “ever exposed” if he had at least one job with a non-zero probability of exposure. The cumulative duration of exposure was defined as the sum of all exposure durations. The CEI was calculated as the sum of the values obtained by multiplying the weighted duration, probability, intensity, and frequency of exposure for each exposure period in the entire professional life.

Statistical analysis

Unconditional multivariable logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (95% CI) for tobacco and alcohol consumption, BMI, personal and family history of cancer, occupations, industries, and several occupational exposures. All ORs were minimally adjusted for age (quartiles, <51, 51–59.5, 59.6–62.2, ≥62.3), sex, and area of residence (10 *départements*). Additional adjustments were made for tobacco use, personal history of HNC, and socioeconomic status assessed by the longest occupational class held. Because these adjustments did not impact results significantly though they increased the number of parameters to be estimated, the ORs were not adjusted for these variables.

ORs were calculated for each of the 3-, and 5-digit ISCO occupation codes, 2- and 4-digit NAF industry codes (ever/never worked), and for parameters of exposures under study (ever/never exposed, cumulative duration, and CEI). Cutoff points were used to categorize cumulative duration (10 years) and CEI (median of the distributions among controls). In all analyses, the "never exposed" group was used as the reference category. Dose-response relationship between the risk of SGC and each variable analyzed was explored by a test for trend, performed only when the linearity assumption was satisfied. We present here the results for occupations, industries, and nuisances with at least three exposed cases.

All tests were two-sided, and a p value ≤0.05 was considered statistically significant. Statistical analyses were conducted using STATA software version 12.0 (StataCorp, TX, USA).

Results

Compared to controls, cases were more likely to be women, younger, and with a lower socioeconomic status and educational level (Table 1). Among the 73 cases, parotid glands were the most affected location (52.1%) and the most frequent histological type was adenoid cystic carcinoma (21.9%).

Table 1 Main characteristics of cases and controls and tumor location. The ICARE study.

	Cases	Controls	p[a]
	n = 73 (%)	n = 3555 (%)	
Gender			0.005
Male	47 (64.4)	2780 (78.2)	
Female	26 (35.6)	775 (21.8)	
Age (quartiles)			0.09
Mean (SD)	56.9 (11.9)	58.5 (10.2)	
<51	18 (24.7)	892 (25.1)	
51–59.5	25 (34.2)	882 (24.8)	
59.6–62.2	10 (13.7)	906 (25.5)	
≥62.3	20 (27.4)	875 (24.6)	
Area of residence			0.25
Calvados	7 (9.6)	462 (12.9)	
Doubs, Territoire du Belfort	1 (1.4)	143 (4.0)	
Herault	12 (16.4)	450 (12.7)	
Isere	4 (5.5)	501 (14.1)	
Loire Atlantique	12 (16.4)	404 (11.4)	
Manche	6 (8.2)	312 (8.8)	
Bas-Rhin	9 (12.3)	469 (13.2)	

Haut-Rhin	4 (5.5)	118 (3.4)	
Somme	11 (15.1)	499 (14.0)	
Vendée	7 (9.6)	197 (5.5)	
Socioeconomic status (based on the longest job held)			0.10
Manager	7 (9.6)	618 (17.4)	
Farmer	6 (8.2)	197 (5.5)	
Self-employed workers	7 (9.6)	177 (4.9)	
Intermediate white-collar workers	9 (12.3)	695 (19.5)	
Office and sales employees	16 (21.9)	672 (18.9)	
Blue-collar workers	27 (37)	1178 (33.1)	
Educational level			0.11
Primary or less	18 (24.7)	763 (21.5)	
Vocational secondary	28 (38.4)	1351 (38.0)	
General secondary	7 (9.6)	400 (11.3)	
University	12 (16.4)	901 (25.3)	
Others	2 (2.7)	23 (0.6)	
Tumor location[b]			
Parotid gland (C07.9)	38 (52.1)		
Submandibular gland (C08.0)	9 (12.3)		
Sublingual gland (C08.1)	1 (1.3)		
Major salivary gland, unspecified (C08.9)	4 (5.5)		
Minor salivary glands	21 (28.8)		
Histological type[c]			
Adenoid cystic carcinoma (8200)	16 (21.9)		
Mucoepidermoid carcinoma (8430)	11 (15.0)		
Squamous cell carcinoma (major salivary glands) (8070, 8071)	10 (13.7)		
Adenocarcinoma not otherwise specified (8140)	9 (12.3)		
Carcinoma ex pleomorphic adenoma (8941)	4 (5.5)		
Mucinous adenocarcinoma (8480)	3 (4.1)		
Epithelial myoepithelial carcinoma (8562)	3 (4.1)		
Others	17 (23.3)		

SD = standard deviation.

[a] *p* values are derived from the Pearson's chi-square test for categorical variables or Student's test for continuous variables.

[b] Topographical codes of the International Classification of Diseases for Oncology (ICD-O-3).

[c] Morphological codes of the ICD-O-3.

Although elevated risks of SGC were found for current smokers, quantity >15.7 g/day, duration >25 years, and cumulative quantity >16.5 pack-years, the results were not significant (Table 2). In addition, no trends were found. Analysis stratified by type of salivary gland (major and minor) showed significant ORs for major SGC associated with current smoking (OR = 2.37, 95% CI: 1.13–4.98), and duration >35 years (OR = 3.08, 95% CI: 1.38–6.90), but no trend emerged. No association was found between minor SGC and tobacco consumption (not shown).

Table 2 Risk of salivary gland cancer associated with tobacco smoking. The ICARE study.

		Cases	Controls	OR[a] (95% CI)	p trend
		n = 73 (%)	n = 3555 (%)		
Smoking status					
Never smoker		27 (36.9)	1262 (34.5)	Reference	
Former smoker		23 (31.5)	1461 (41.1)	0.98 (0.53–1.79)	
Current smoker		23 (31.5)	820 (23.1)	1.63 (0.88–3.01)	
Quantity (g/day, quartiles)					
Never smoker		27 (36.9)	1262 (34.5)	Reference	0.66
Ever smoker					
Mean (SD)		16.9 (12.5)	17.8 (14.2)		
1–8.7		12 (16.4)	563 (15.8)	1.20 (0.59–2.44)	
8.7–15.7		10 (13.7)	564 (15.9)	1.02 (0.47–2.19)	
15.7–21.7		13 (17.8)	561 (15.7)	1.48 (0.72–3.03)	
>21.7		11 (15.1)	563 (15.8)	1.31 (0.61–2.83)	
Duration (years, quartiles)					
Never smoker		27 (36.9)	1262 (34.5)	Reference	0.49
Ever smoker					
Mean (SD)		27.7 (13.8)	25.1 (13.3)		
1–15		12 (16.4)	611 (17.2)	1.12 (0.54–2.30)	
16–25		4 (5.5)	560 (15.8)	0.41 (0.14–1.23)	
26–35		15 (20.5)	554 (15.6)	1.59 (0.80–3.16)	
>35		15 (20.5)	555 (15.6)	1.86 (0.92–3.73)	

Cumulative quantity (pack-years, quartiles)					
Never smoker		27 (36.9)	1262 (34.5)	Reference	0.40
Ever smoker					
Mean (SD)		24.0 (24.1)	20.6 (19.4)		
1–6.4		13 (17.8)	561 (15.7)	1.28 (0.64–2.59)	
6.5–16.5		6 (8.2)	571 (16.1)	0.64 (0.25–1.60)	
16.5–29		12 (16.4)	562 (15.8)	1.35 (0.64–2.81)	
>29		14 (19.2)	554 (15.6)	1.68 (0.82–3.42)	

SD = standard deviation; OR = odds ratio; CI = confidence interval.

[a] ORs were adjusted for age, sex, and area of residence.

Slightly increased, although non-significant ORs were found among drinkers of ≥4 glasses/day and for a cumulative consumption of ≥118.3 glass-years (Table 3). Nevertheless, the tests for trend were not significant. Analyses by type of salivary glands showed similar results for major SGC, but no associations with minor SGC were found (not shown).

Table 3 Risk of salivary gland cancer associated with alcohol consumption. The ICARE study.

	Cases	Controls	OR [a] (95% CI)	*p* trend
	n = 73	n = 3555		
Drinking status				
Never drinker	9	306	Reference	
Former drinker	6	156	1.34 (0.45–3.97)	
Current drinker	56	3071	0.68 (0.31–1.46)	
Quantity (glass/day, quartiles)				
Never drinker	9	306	Reference	0.16
Ever drinker				
0.03–0.44	13	813	0.53 (0.22–1.28)	
0.45–1.75	12	804	0.54 (0.21–1.38)	
1.76–3.95	14	807	0.75 (0.30–1.89)	
>3.95	22	799	1.37 (0.55–3.37)	
Duration (years, quartiles)				
Never drinker	9	306	Reference	0.36
Ever drinker				
1–29	17	864	0.66 (0.26–1.66)	

30–38	17	766	0.72 (0.29–1.77)	
39–46	16	797	0.92 (0.37–2.29)	
≥47	12	791	0.64 (0.23–1.80)	
Cumulative quantity (glass-years, quartiles)				
Never drinker	9	306	Reference	0.41
Ever drinker				
0.03–9.0	14	805	0.57 (0.24–1.38)	
9.1–47	12	807	0.52 (0.21–1.32)	
47.1–118.2	16	803	0.83 (0.33–2.06)	
≥118.3	19	800	1.17 (0.46–2.96)	

SD = standard deviation; OR = odds ratio; CI = confidence interval.

[a] ORs were adjusted for age, sex, and area of residence.

Table 4 depicts the associations between the risk of SGC and other non-occupational risk factors. BMI at interview was inversely associated with the risk of SGC; compared with normal weight subjects, the risk was significantly higher in underweight subjects and significantly lower in overweight and obese subjects. No significant association was observed between the risk of SGC and BMI 2 years prior to the interview/diagnosis or that at age 30. Similar results were observed for major SGCs, but no associations were found for minor SGCs (not shown).

Table 4 Risk of salivary gland cancer associated with body mass index, history of cancer and of radiation therapy, and family history of head and neck cancer. The ICARE study.

	Cases	Controls	OR [a] (95% CI)	*p* trend
	n = 73	n = 3555		
BMI at interview/diagnosis				
<18.5	4	37	**3.55 (1.14–11.0)**	
18.5–24.9	31	1328	Reference	0.005
25–29.9	26	1441	0.77 (0.44–1.32)	
≥30	8	573	0.57 (0.26–1.28)	
BMI 2 years prior the interview/diagnosis				
<18.5	0	37	–	
18.5–24.9	26	1367	Reference	0.56
25–29.9	29	1367	1.18 (0.68–2.05)	
≥30	10	577	0.94 (0.44–2.00)	
BMI at age 30				
<18.5	3	97	1.36 (0.40–4.65)	

18.5–24.9	41	2351	Reference	0.45
25–29.9	16	672	1.42 (0.78–2.57)	
≥30	2	123	0.99 (0.23–4.20)	
Previous history of cancer				
No	60	3090	Reference	
Yes				
All cancer locations	8	291	1.40 (0.64–3.03)	
Head and neck cancer	3	13	**17.06 (4.34–67.05)**	
Prostate cancer	1	78	0.74 (0.10–5.64)	
Hematological cancer	1	16	2.85 (0.35–23.08)	
Other cancer locations	3	184	0.73 (0.22–2.41)	
History of radiation therapy for cancer				
No	65	3265	Reference	
Yes				
All cancer locations	2	106	0.81 (0.19–3.43)	
Head and neck cancer	1	2	**31.74 (2.48–405.25)**	
Hematological cancer	1	8	5.10 (0.56–46.20)	
Other cancer locations	0	96	–	
Family history of head and neck cancer				
No	56	2891	Reference	
≥1 first-degree relative	4	166	1.18 (0.42–3.34)	

BMI = body mass index; OR = odds ratio; CI = confidence interval.

[a] ORs were adjusted for age, sex, and area of residence.

A history of cancer (all locations) elevated the risk of SGC slightly, while a history of HNC increased the risk strongly. Exposure to radiotherapy for HNC treatment was associated with a strong and significant OR. The results were consistent for major and minor salivary glands (not shown).

A family history of HNC in first-degree relatives was not significantly associated with a risk of SGC.

Table 5 shows the associations between the risk of SGC and occupations. Significantly elevated ORs were found for waiters, bartenders, and related workers; charworkers, cleaners, and related workers; electrical and electronic equipment assemblers; plumbers and pipe fitters; welders (particularly electric arc welders) and flame cutters; sheet-metal workers; building painters; and material handling equipment operators. In addition, increased risks ($OR > 1.5$, $p < 0.15$) were observed for postmen, working proprietors (retail trade), cooks, maids and related housekeeping service workers, general and dairy farm workers, and truck and van drivers (long-distance transport).

Table 5 Risk of salivary gland cancer associated with selected occupations according to the International Standard Classification of Occupations (ISCO, 1968). The ICARE study.

Occupation (ISCO codes)[b]	Exposed cases/controls	OR[a] (95% CI)
Secondary education teachers (1–32)	4/227	0.86 (0.31–2.41)
Primary education teachers (1–33)	3/131	0.96 (0.29–3.13)
Teachers n.e.c (1–39)	3/125	1.41 (0.43–4.60)
Stenographers, typists and teletypists (3–21)	3/140	0.67 (0.20–2.25)
Bookkeepers and cashiers (3–31)	4/228	0.69 (0.24–1.94)
Mail distribution clerks (3–70)	3/97	1.45 (0.44–4.78)
Postman (3–70.30)	3/45	3.33 (0.98–11.28)
Working proprietors (wholesale and retail trade) (4–10)	4/111	1.81 (0.64–5.14)
Working proprietor (retail trade) (4–10.30)	4/97	2.07 (0.73–5.88)
Salesmen, shop assistants and demonstrators (4–51)	3/227	0.47 (0.14–1.55)
Working proprietors (catering and lodging services) (5–10)	3/59	2.33 (0.70–7.74)
Cooks (5–31)	5/104	2.04 (0.79–5.27)
Other cooks (5–31.90)	3/47	2.36 (0.69–8.01)
Waiters, bartenders and related workers (5–32)	6/96	**2.61 (1.07–6.35)**
Waiter, general (5–32.10)	5/71	**2.94 (1.11–7.78)**
Maids and related housekeeping service workers n.e.c (5–40)	8/144	1.96 (0.84–4.56)
Housemaid (5–40.20)	4/73	1.81 (0.60–5.47)
Nursemaid (5–40.35)	3/50	1.75 (0.50–6.10)
Charworkers, cleaners and related workers (5–52)	10/164	**2.47 (1.16–5.22)**
Charworker (5–52.20)	10/138	**3.02 (1.38–6.60)**
General farmers (6–11)	3/87	1.65 (0.49–5.56)
Specialised farmers (6–12)	3/169	0.85 (0.26–2.79)
General farm workers (6–21)	5/218	1.11 (0.43–2.89)
Farm worker (general) (6–21.05)	5/133	1.97 (0.74–5.18)
Dairy farm workers (6–25)	4/109	2.21 (0.74–6.58)
Dairy farm worker (general) (6–25.10)	4/106	2.29 (0.77–6.81)
Blacksmiths, toolmakers and machine-tool operators n.e.c (8–39)	3/77	2.15 (0.65–7.12)
Electrical and electronic equipment assemblers (8–53)	3/25	**7.16 (2.02–25.38)**
Plumbers and pipe fitters (8–71)	5/81	**3.51 (1.33–9.29)**
Plumber (general) (8–71.05)	4/54	**3.95 (1.33–11.67)**
Welders and flame cutters (8–72)	6/77	**4.55 (1.86–11.12)**

Electric arc welder (hand) (8–72.20)	3/30	**6.15 (1.76–21.48)**
Sheet-metal workers (8–73)	4/90	**2.89 (1.01–8.32)**
Painters, construction (9–31)	3/61	2.91 (0.87–9.75)
Building painter (9–31.20)	3/52	**3.42 (1.01–11.49)**
Construction workers n.e.c (9–59)	4/147	1.55 (0.54–4.43)
Dockers and freight handlers (9–71)	5/196	1.26 (0.49–3.13)
Material handling equipment operators n.e.c (9–79)	4/49	**5.05 (1.71–14.84)**
Motor-vehicle drivers (9–85)	6/286	1.18 (0.50–2.79)
Lorry and van driver (long-distance transport) (9–85.60)	4/89	2.54 (0.88–7.30)
Labourers n.e.c (9–99)	4/136	1.68 (0.59–4.74)

OR = odds ratio; CI = confidence interval; n.e.c = not elsewhere classified.

[a] ORs were adjusted for age, sex, and area of residence.

[b] Only ISCO codes with at least 3 exposed cases are presented in this table.

Increased risks of SGC were observed for several industries (Table 6). The risks were significantly elevated for growing of cereals and other crops, manufacture of furniture, interurban freight transports by road, and industrial cleaning. The increased risk found for hotels and restaurants was limited to canteens. Non-significantly elevated risks ($OR > 1.5$, $p < 0.20$) were observed for cattle and dairy farming; manufacture of motor vehicles; recreational, cultural, and sporting activities; other service activities; and household activities such as employers of domestic staff.

Table 6 Risk of salivary gland cancer associated with selected industries according to the French classification of activities (NAF, 1999). The ICARE study.

Industry (NAF codes)[b]	Exposed cases/controls	OR[a] (95% CI)
Agriculture, hunting and related service activities (01)	15/555	1.44 (0.77–2.56)
Growing of cereals and other crops n.e.c. (01.1A)	4/46	**5.15 (1.71–15.44)**
Cattle farming, dairy farming (01.2A)	3/90	2.36 (0.68–9.51)
Growing of crops combined with farming of animals (01.3Z)	6/299	0.92 (0.38–2.22)
Manufacture of food products and beverages (15)	4/320	0.57 (0.20–1.58)
Manufacture of basic metals (27)	3/78	2.08 (0.63–6.91))
Manufacture of fabricated metal products, except machinery and equipment (28)	3/241	0.65 (0.20–2.11)
Manufacture of machinery and equipment n.e.c. (29)	4/259	0.87 (0.31–2.45)
Manufacture of motor vehicles, trailers and semi-trailers (34)	5/201	1.70 (0.65–4.43)
Manufacture of motor vehicles (34.1Z)	4/120	2.52 (0.86–7.38)
Manufacture of other transport equipment (35)	5/125	2.06 (0.78–5.38)
Manufacture of furniture; manufacturing n.e.c. (36)	6/123	**2.77 (1.15–6.67)**
Construction (45)	13/584	1.35 (0.71–2.57)

Wholesale trade and commission trade, except of motor vehicles and motorcycles (51)	4/289	0.72 (0.26–2.02)
Retail trade, except of motor vehicles and motorcycles; repair of personal and household goods (52)	12/462	1.16 (0.61–2.20)
Hotels and restaurants (55)	11/233	**2.21 (1.12–4.33)**
Traditional style restaurants (55.3A)	3/86	1.53 (0.46–5.04)
Canteens (55.5A)	3/29	**4.03 (1.14–14.18)**
Land transport; transport via pipelines (60)	5/244	1.14 (0.45–2.90)
Interurban freight transports by road (60.2 M)	4/77	**3.17 (1.10–9.12)**
Post and telecommunications (64)	3/161	0.89 (0.27–2.90)
National post activities (64.1A)	3/122	1.16 (0.35–3.77)
Other business activities (74)	8/371	1.01 (0.47–2.15)
Industrial cleaning (74.7Z)	5/59	**3.40 (1.26–9.13)**
Public administration and defence; compulsory social security (75)	21/1319	0.76 (0.43–1.33)
Defence activities (75.2C)	19/115	0.95 (0.51–1.74)
Education (80)	23/1018	1.15 (0.68–1.93)
Primary education (80.1Z)	4/156	1.00 (0.35–2.83)
General secondary education (80.2A)	3/282	0.49 (0.15–1.57)
Technical and vocational secondary education (80.2C)	10/458	1.15 (0.56–2.34)
Adult training and continuing education (80.4C)	4/131	1.57 (0.55–4.47)
Recreational, cultural and sporting activities (92)	4/113	1.80 (0.64–5.10)
Other service activities (93)	3/48	2.74 (0.81–9.23)
Activities of households as employers of domestic staff (95)	7/121	2.09 (0.86–5.07)
Activities of households as employers of domestic staff (95.0Z)	7/121	2.09 (0.86–5.07)

OR = odds ratio; CI = confidence interval; n.e.c = not elsewhere classified.

[a] ORs were adjusted for age, sex, and area of residence.

[b] Only NAF codes with at least 3 exposed cases are presented in this table.

The risks of SGC associated with occupational exposures assessed with JEMs are presented in Table 7. No significant association was observed for exposure to chlorinated solvents, namely methylene chloride and trichloroethylene. Fewer than three cases were exposed to carbon tetrachloride, chloroform, or perchloroethylene. Exposure to petroleum or oxygenated solvents was not globally associated with the risk of SGC, even though some ORs were slightly increased. However, no dose-response trend emerged for any solvent.

Table 7 Risk of salivary gland cancer associated with occupational exposures assessed through job-exposure matrices. The ICARE study.

Exposures	Never exposed		Ever exposed [b]		Duration of exposure				Cumulative Exposure Index			
					<10 years		≥10 years		< median		≥ median	

	Cases/Controls	OR[a] (95% CI)	Cases/Controls	OR[a] (95% CI)	Cases/Controls	OR[a] (95% CI)	Cases/Controls	OR[a] (95% CI)	Cases/Controls	OR[a] (95% CI)	Cases/Controls	OR[a] (95% CI)
Chlorinated solvents												
Methylene chloride	67/3253	1 (reference)	5/276	0.99 (0.39–2.51)	3/162	1.0 (0.31–3.27)	2/114	0.96 (0.23–4.04)	3/138	1.16 (0.35–3.78)	2/138	0.81 (0.19–3.39)
Trichloroethylene	51/2449	1 (reference)	22/1084	1.22 (0.71–2.11)	9/544	0.97 (0.46–2.03)	13/540	1.51 (0.78–2.94)	12/542	1.27 (0.65–2.47)	10/542	1.17 (0.56–2.41)
At least one	51/2397	1 (reference)	22/1137	1.13 (0.66–1.95)	8/557	0.82 (0.38–1.79)	14/580	1.46 (0.77–2.78)	9/568	0.91 (0.43–1.91)	13/569	1.38 (0.71–2.65)
Petroleum solvents												
Diesel, fuels and kerosene	50/2551	1 (reference)	22/979	1.53 (0.87–2.69)	12/507	1.55 (0.78–3.08)	10/472	1.50 (0.72–3.13)	12/488	1.67 (0.84–3.30)	10/491	1.39 (0.67–2.90)
Benzene	60/2914	1 (reference)	13/618	1.21 (0.65–2.28)	9/394	1.29 (0.62–2.66)	4/224	1.07 (0.37–3.05)	9/309	1.63 (0.79–3.36)	4/309	0.77 (0.27–2.17)
White-spirits	41/2009	1 (reference)	32/1529	1.12 (0.69–1.82)	14/650	1.08 (0.58–2.02)	18/878	1.17 (0.65–2.08)	15/764	0.98 (0.53–1.79)	17/764	1.32 (0.72–2.42)
Other aliphatic mineral spirits	68/3239	1 (reference)	4/294	0.69 (0.25–1.93)	4/147	1.37 (0.48–3.84)	0/147	–	4/147	1.43 (0.51–4.04)	0/147	–
Gasoline	60/2994	1 (reference)	12/535	1.37 (0.71–2.67)	8/308	1.55 (0.71–3.38)	4/227	1.12 (0.39–3.20)	7/267	1.60 (0.70–3.66)	5/268	1.15 (0.44–2.97)
At least one	35/1783	1 (reference)	38/1755	1.26 (0.78–2.04)	12/655	0.98 (0.50–1.92)	26/1099	1.47 (0.86–2.52)	17/876	1.04 (0.57–1.88)	21/878	1.58 (0.88–2.86)
Oxygenated solvents												
Ethylene glycol	68/3332	1 (reference)	4/196	1.11 (0.39–3.15)	2/104	1.00 (0.23–4.23)	2/92	1.25 (0.29–5.25)	2/99	1.03 (0.24–4.36)	2/97	1.20 (0.28–5.08)
Ketones and esters	58/2815	1 (reference)	15/717	1.15 (0.63–2.07)	7/377	0.96 (0.43–2.16)	8/340	1.38 (0.64–2.96)	6/359	0.91 (0.38–2.16)	9/358	1.38 (0.67–2.87)
Alcohols	42/2234	1 (reference)	31/1299	1.15 (0.71–1.87)	13/612	0.99 (0.52–1.87)	18/685	1.32 (0.75–2.34)	11/641	0.84 (0.43–1.66)	20/656	1.46 (0.84–2.54)
At least one	36/1735	1 (reference)	37/1799	0.98 (0.61–1.57)	15/724	0.94 (0.51–1.75)	22/1074	1.01 (0.59–1.74)	14/818	0.76 (0.40–1.43)	23/900	1.19 (0.69–2.03)
Other nuisances												
Asbestos	41/1786	1 (reference)	32/1769	0.96 (0.57–1.59)	12/567	1.06 (0.54–2.08)	20/1202	0.90 (0.50–1.62)	14/884	0.81 (0.42–1.52)	18/885	1.15 (0.62–2.13)
Mineral wool	53/2619	1 (reference)	19/914	0.81 (0.45–1.44)	11/444	1.55 (0.77–3.14)	8/470	1.03 (0.46–2.28)	12/457	1.66 (0.84–3.28)	7/457	0.92 (0.40–2.13)
Silica	57/2881	1 (reference)	15/649	1.55 (0.83–2.90)	7/327	1.39 (0.61–3.20)	8/322	1.72 (0.78–3.80)	7/327	1.43 (0.62–3.28)	8/322	1.68 (0.76–3.71)

Cement	57/2990	1 (reference)	15/539	1.86 (0.99–3.48)	11/273	**2.61 (1.29–5.27)**	4/266	1.04 (0.36–2.98)	9/269	**2.19 (1.03–4.65)**	6/270	1.52 (0.62–3.69)
Refractory ceramic fibers	67/3272	1 (reference)	5/267	1.04 (0.40–2.67)	0/115	–	5/152	1.85 (0.71–4.80)	1/134	0.41 (0.06–3.05)	4/133	1.67 (0.58–4.79)

Cutoff point for Cumulative Exposure Index: median value of exposed controls.

[a] ORs were adjusted for age, sex, and area of residence.

Overall, the risks were not increased among subjects exposed to asbestos, mineral wool, and refractory ceramic fibers. Ever exposure to silica was associated with a non-significantly increased risk of SGC, and the ORs increased with the duration and cumulative level of exposure. However, the tests for trend were not significant. A borderline significant association was observed with ever exposure to cement, but the highest ORs were observed for shorter durations and for the lower category of CEI. Because subjects exposed to cement are generally co-exposed to silica, we performed additional adjustments for silica. All significant associations observed for cement exposure were rendered non-significant. Additional analysis was performed on subjects exclusively exposed to cement (4 cases, 98 controls), exclusively exposed to silica (4 cases, 207 controls), and exposed to both nuisances (11 cases, 441 controls) (reference category: never exposed to cement, never exposed to silica). The corresponding ORs were 2.50 (95% CI: 0.88–7.55), 1.46 (95% CI: 0.50–4.23), and 1.83 (95% CI: 0.88–3.78), respectively.

Discussion

The ICARE study is one of the few studies worldwide and the first study in France to explore a wide range of non-occupational and occupational risk factors for SGC. We found significantly increased risks associated with a history of HNC and HNC-related radiotherapy, and elevated risks (non-significant) associated with tobacco use.

Consistent with literature [6,10,11,13,23,24,43,44], our results do not support an association between tobacco smoking and SGC. Elevated, though non-significant risks were found (and no dose-response relation observed) for current smokers, for duration >25 years and for consumption >16.5 pack-years. Similarly, consistent with literature, no association between SGC and alcohol consumption was found [3,10–13,23,43,44].

Unlike in other studies [9,10], in our study, a previous history of cancer overall was not associated with the risk of SGC, though a prior history of HNC significantly increased the risk. This may be due to the use of radiotherapy, a well-known risk factor for SGC, in HNC treatment [4,6,9,10]. Consistent with these results, but based only on three exposed subjects, we found an elevated risk of SGC among radiotherapy-treated HNC patients.

Similar to a prior study [44], high BMI was not associated with an increased risk of SGC in our study. These findings are contrary to those of two other studies [13,23] which suggested a possible increased risk of SGC in obese subjects, although the results were not significant. In our study, having a family history of HNC among first-degree relatives did not increase the risk of SGC, unlike that in one study [13] which found a slight, non-significantly increased risk.

Agricultural work was associated with an increased risk of SGC in several studies [10,17,45]. Similarly, in our study, occupations such as general farm worker, dairy farm worker, and industries such agriculture (cereals and other crops) and cattle and dairy farming were associated with elevated risks of SGC, with ORs >2.

Significantly elevated risks of SGC have been reported previously among hairdressers [6,19,20], beauty shop employees [20], rubber industry workers [4,15,46], and among those occupationally exposed to radiation or radioactive materials [4,13,45]. In the present study, we were unable to assess these occupations adequately due to a small sample size or lack of exposed cases (only one case and 23 controls were hairdressers, barbers, beauticians, and related workers; there were no cases of rubber industry workers and radiation-exposed workers).

Increased risk of SGC was observed in occupational workers such as woodworkers in the automotive industry [18] and machine repairers [20]. In the present study, manufacturing of motor vehicles and manufacturing of furniture were associated with elevated risks of SGC (2.5-fold for motor vehicle manufacturing (non-significant), 2.7-fold for furniture manufacturing (significant)). We were unable to carry out more in-depth analysis because of the small number of subjects (<3) in each 4-digit industrial sector.

In close agreement with a previous study conducted in the United States [45], in our study, several occupations (waiter, bartender, and food service-related worker; charworker, cleaner, and sanitation-related worker; and electrical and electronic equipment assembler) and industries (canteens, interurban freight transports by road, and industrial cleaning) were associated with a significantly higher risk of SGC. Occupations such as cook, housemaid, and postman, and industries such as household services (as employers of domestic staff) were associated with an increased risk of SGC (ORs, approximately 2; non-significant).

Our results suggest a possible link between SGC and occupational exposure to cement and silica, though the sample size was small and the results were not significant. Two prior studies have reported a significant association between the risk of SGC and exposure to cement [12] or silica [11] dust. Asbestos exposure was associated with elevated risks of SGC in two studies [12,14], but not in our study.

Literature reports link exposure to metals in the plumbing industry [16], to nickel compounds and alloys [4,12], and to chromium [12] with an increasing incidence of and mortality from SGC. We were not able to analyze the exposure to these metals in our study. Nevertheless, the following occupations leading to exposure to metals were found to be associated with increased risks of SGC: electrical and electronic equipment assembler, plumber, pipe-fitter, welder, flame-cutter, sheet-metal worker, blacksmith, toolmaker, and machine-tool operator. Solvent-exposed workforce such as charworkers, cleaners, and painters were also found to have elevated risks of SGC in the present study. However, the analysis of solvent exposure through JEMs did not show significant associations with the risk of SGC, although ORs were slightly elevated for some chlorinated, oxygenated and petroleum solvents (e.g., trichloroethylene; ketones and esters; diesel, fuels and kerosene). One study found a significantly elevated risk of SGC among subjects using kerosene as cooking fuel, and a non-significantly increased risk related to exposure to petroleum products but not to benzene paints [11]. In another study, solvent exposure estimated with a JEM was associated with a higher SGC-related mortality rate (20% to 40% higher), although the test for trend was not statistically significant [45].

The strengths of the ICARE study design include a detailed questionnaire administered during in-person interviews by trained interviewers, uniform coding methods for occupations and industries, and use of JEMs for assessing occupational exposure.

A collaboration with the French network of cancer registries allowed for recruitment of almost all SGC cases in the covered geographical areas. The randomly selected control group showed a representative distribution of socioeconomic characteristics, and lifelong exposure to alcohol, tobacco, and to other substances studied [42]. Participation rates were satisfactory (>80% in cases and controls), suggesting that selection bias, if present, was minimal.

Our study has some limitations. Recall bias may have occurred because of self-reported non-professional and professional data. However, it is unlikely that this bias would be different between cases and controls because occupational exposures are not widely known to be risk factors for SGC. Moreover, this bias may be minimal because the average number of jobs (cases, 3.9; controls, 4.3) and the duration of the working life (cases, 31.9 years; controls, 33.7 years) were comparable between groups.

Coding occupations and industries is difficult and often not reproducible. However, coders received special training and were blind to case-control status. Therefore, if coding errors occurred, they were probably not different between groups. Exposures were not assessed on direct measurements collected at an individual level but were estimated through job titles, which do not take into account the variability of exposure within the same job, depending on the tasks performed. Moreover, the imprecision of exposure assessment with JEMs, based on job-specific averages, could have led to a non-differential misclassification bias, which generally results in an estimation of the risk biased toward the null value for dichotomized exposures [47] and a distortion of exposure-response trends [48]. This may explain why for some nuisances (e.g., cement, some petroleum solvents), we found higher estimates only for the lowest category of duration or CEI and no dose-response relation.

The small number of subjects in some subgroups may have resulted in a lack of statistical power. We assessed a large number of associations, and made multiple comparisons, which may have led to statistically significant associations which may have been due to chance alone. However, we retained only the results consistent with literature and those for which there was a concordance between occupations and industries or between occupations/industries and possible exposures.

Conclusion

This study provided evidence of the association of SGC with a history of HNC and of cervicofacial radiotherapy, occupational history, and specific occupation- and industry-related exposures. However, further analyses on larger samples are required to confirm our results.

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Conflict of interest

All authors declare that they have no conflict of interest.

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Highlights

- Tobacco and alcohol consumption did not increase the risk of salivary gland cancer.
- History of head and neck cancer and cervicofacial radiotherapy increased the risk.

- Several occupations and industries were associated with elevated risks.
- Statistical power was limited for in-depth analyses.

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