

BMJ Open Occupational exposure to solvents and risk of head and neck cancer in women: a population-based case-control study in France

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ABSTRACT

Objective: Our objective was to investigate the association between head and neck cancer and occupational exposure to chlorinated, oxygenated and petroleum solvents in women.

Methods: Investigation of occupational and environmental CAuses of REspiratory cancers (ICARE), a French population-based case-control study, included 296 squamous cell carcinomas of the head and neck (HNSCC) in women and 775 female controls. Lifelong occupational history was collected. Job-exposure matrices allowed to assess exposure to 5 chlorinated solvents (carbon tetrachloride; chloroform; methylene chloride; perchloroethylene; trichloroethylene), 5 petroleum solvents (benzene; special petroleum product; gasoline; white spirits and other light aromatic mixtures; diesel, fuels and kerosene) and 5 oxygenated solvents (alcohols; ketones and esters; ethylene glycol; diethyl ether; tetrahydrofuran). OR and 95% CIs, adjusted for smoking, alcohol drinking, age and geographical area, were estimated with logistic models.

Results: Elevated ORs were observed among women ever exposed to perchloroethylene (OR=2.97, 95% CI 1.05 to 8.45) and trichloroethylene (OR=2.15, 95% CI 1.21 to 3.81). These ORs increased with exposure duration (OR=3.75, 95% CI 0.64 to 21.9 and OR=4.44, 95% CI 1.56 to 12.6 for 10 years or more, respectively). No significantly increased risk of HNSCC was found for occupational exposure to the other chlorinated, petroleum or oxygenated solvents.

Conclusions: These findings suggest that exposure to perchloroethylene or trichloroethylene may increase the risk of HNSCC in women. In our study, there is no clear evidence that the other studied solvents are risk factors for HNSCC.

INTRODUCTION

Compared with other European Union countries, head and neck cancers are frequent in France.¹ Age-standardised (world population) incidence rates in 2012 in France were 16.1

Strengths and limitations of this study

- Little is known about occupational risk factors for head and neck cancer in women. Our study is one of the largest studies on this topic.
- The study was population-based; exposure to solvents was assessed from the entire occupational history, obtained from in-person interviews.
- Special attention was paid to adjustment for alcohol and tobacco consumption.
- Exposure assessment through job-exposure matrices may entail misclassification of exposure, which is likely to be non-differential.
- Despite a relatively large number of cases, statistical power was limited for in-depth analyses by cancer sites.

per 100 000 for lip, oral cavity and pharynx (LOCP) cancers and 5.4 per 100 000 for laryngeal cancer in men, and 5.6 per 100 000 for LOCP and 0.9 per 100 000 for laryngeal cancer in women. Moreover, in 1980–2012, the incidence of LOCP cancer and laryngeal cancer increased by 60% and 50%, respectively, in women, while it decreased by 60% and 62%, respectively, in men.²

Tobacco smoking and alcohol consumption are well established major risk factors for these cancers,³ and the joint effect of tobacco and alcohol is at least multiplicative.⁴

In addition to these major risk factors, several studies have investigated the role of occupational exposures in the occurrence of head and neck cancers. Thus, some occupations in men^{5–17} and women^{14 18–21} were associated with the risk of developing head and neck cancer.

In a previous analysis by occupation among women,²² we found a high risk of head and neck cancer associated with various

occupations and industries, among them electrical and electronic equipment assemblers, radio, television and communication equipment manufacturing, flame cutters, welders and printers, which suggested a possible role of exposure to solvents. Some studies have shown an increased risk of head and neck cancer associated with exposure to solvents.^{23 24} Some solvents such as trichloroethylene (TCE),²⁵ perchloroethylene (PCE)²⁵ or benzene²⁶ are classified as proven or probable carcinogens by International Agency for Research on Cancer (IARC), but for cancer sites other than head and neck.

The majority of results on the association between solvent exposures and cancers of the upper aerodigestive tract were observed in studies conducted in men and very few studies were conducted among women. However, chlorinated and oxygenated solvents are commonly used by women.²⁷ In addition, circumstances of exposure can vary between men and women and some studies have suggested gender differences in the toxicokinetics of solvents.^{28 29} Investigation of occupational and environmental CAuses of REspiratory cancers (ICARE), one of the largest population-based case-control studies of head and neck cancer, offers the opportunity to study the association between cancer of the head and neck and occupational exposures to chlorinated, oxygenated and petroleum solvents in women.

MATERIALS AND METHODS

Study population

ICARE has been described in detail previously.³⁰ Briefly, ICARE is a multicentre, population-based case-control study, which included a group of 2926 lung cancer cases, a group of 2415 head and neck cancer cases and a common control group of 3555 subjects. Incident cases were identified in collaboration with cancer registries in 10 geographical areas in France. All incident primary cancer cases of the head and neck diagnosed between 2001 and 2007 were included, comprising malignant neoplasms of the LOCP (C00-C14), nasal cavity and accessory sinuses (C30.0, C31) and larynx (C32) as coded by the International Classification of Diseases for Oncology, third edition (ICD-O-3). Included cases were histologically confirmed cases, aged 18 years to 75 years at diagnosis. All histological types were included. The control group was a random sample of the population of the same geographical areas, with a distribution by sex and age comparable to that of head and neck cancer and lung cancer cases, and a distribution by socioeconomic status (SES) comparable to that of the general population. Subjects were interviewed face to face, using a standardised questionnaire collecting information on lifetime tobacco and alcohol consumption, residential history and a detailed description of occupational history. Participation rates were 80.6% among controls and 82.5% among cases.³⁰

Each subject gave written informed consent.

Study sample

Only women were considered in this analysis. In all, 361 female head and neck cancer cases were included in the ICARE study. The present analysis was restricted to squamous cell carcinomas of the following cancer sites: (1) oral cavity, 88 cases (29.7%): ICD-O-3 codes C00.3—C00.9, C02.0—C02.3, C03, C04, C05.0 and C06; (2) oropharynx, 111 cases (37.5%): codes C01.9, C02.4, C05.1, C05.2, C09 and C10; (3) hypopharynx, 28 cases (9.5%): codes C12- C13; (4) oral cavity, pharynx unspecified or overlapping, 22 cases (7.4%): codes C02.8, C02.9, C05.8, C05.9 and C14; (5) larynx, 47 cases (15.9%): codes C32. There were 296 cases and 775 controls in the final study group.

Coding of job titles

Each job held for at least 1 month was coded using the International Standard Classification of Occupations (ISCO)³¹ and the Nomenclature des Activités Françaises (NAF),³² the French classification for industrial activities. Occupational histories were coded by specially trained coders blind as to the case-control status.

Exposure assessment

Occupational exposure to five chlorinated solvents (carbon tetrachloride; chloroform; methylene chloride; PCE; TCE), five petroleum solvents (benzene; special petroleum product; gasoline; white spirits and other light aromatic mixtures; diesel, fuels and kerosene) and five oxygenated solvents (alcohols; ketones and esters; ethylene glycol; diethyl ether; tetrahydrofuran) was assessed using job-exposure matrices (JEMs) developed for the French population by the French Institute of Health Surveillance.³³ For each combination of ISCO and NAF codes, the JEMs assigned three exposure indices: (1) probability of exposure expressed as the percentage of exposed workers, (2) intensity of exposure and (3) frequency of exposure. For these three indices, different categories were used depending on the solvent considered (see online supplementary material table S1).

To account for changes in exposure over time, different indices were provided for different calendar periods from 1947 to 2007. Exposure information for the earliest period was used for jobs held before 1947.

'Ever exposed' to a specific solvent refers to subjects having had at least one job with probability of exposure >0. Cumulative duration of exposure was computed by summing all exposed periods.

Cumulative Exposure Indices (CEIs) were obtained by summing the product of exposure probability, frequency, intensity and duration for each job period, over the lifetime occupational history, using the central value of each of the three classes. We also calculated the average exposure intensity, as the CEI divided by the total duration of exposure.

Statistical analysis

Exposure duration, average exposure intensity and CEI were used as continuous variables. We first used restricted cubic splines (4 knots) to check the linearity assumption. None of the tests for departure from linearity were significant. Exposure variables were also categorised (cut points: 10 years for duration, median of the distributions among controls for average intensity and CEI). In all analyses, 'never exposed' refers to subjects never exposed to a specific solvent and was used as the reference category.

Owing to the low exposure prevalence for most solvents among women, we favoured sensitivity over specificity by using a broad definition of ever exposure (probability >0). We also conducted additional analyses using different cut-off points for probability, in order to increase specificity.

Unconditional logistic regression was used to estimate ORs and corresponding 95% CIs of head and neck cancers. Analyses were adjusted for geographical area (ten 'départements'), age, smoking status (never smoker, former smoker and current smoker), tobacco consumption in pack-years and alcohol consumption in drink-years. Cubic splines were used for alcohol and tobacco because they allowed to better take into account their effects, according to the Bayesian information criterion. Since interactions between smoking status and alcohol consumption, and between smoking status and tobacco consumption, were significant, all models included these interaction terms.

Additional adjustments were made for SES assessed by the last occupation held and by the longest held occupation. Since additional adjustment for SES did not markedly change the results, while it increased the number of parameters to be estimated, the ORs reported in the results section are those not adjusted for SES. Adjustment for asbestos exposure was also performed but did not modify the estimates and these results are not presented here.

ORs were also estimated for each cancer site (as described above: oral cavity, oropharynx, hypopharynx and larynx) using polytomous logistic regression.

Statistical analyses were performed using STATA software (StataCorp LP 2015; V. 13.1). All p values were two-sided and a p value ≤ 0.05 was used as a threshold for statistical significance.

RESULTS

The main characteristics of cases and controls are presented in [table 1](#). On average, cases were 2 years younger than controls. This is explained by the fact that controls were stratified on age (in four categories: <40 years, 40–54 years, 55–64 years and >65 years) based on the age distribution of head and neck cancer cases and lung cancer cases. The SES of cases was lower than that of controls. Cases were less likely to be never smokers or never drinkers than controls. [Table 2](#) shows

the numbers and proportions of cases and controls exposed to the various chlorinated, petroleum and oxygenated solvents. The prevalence of exposure was low (10% or less among controls) for most of the specific solvents, with the exception of white spirits and alcohols, for which 32% and 48% of the controls were exposed, respectively.

Ever exposure to TCE and to PCE was associated with significantly elevated ORs. No other significant association was found. Additional analyses using a more specific cut point to define ever exposure (probability >10% for methylene chloride, probability >30% for TCE, probability >50% for the other solvents) produced similar results, although the CIs were wider due to the smaller number of exposed women (data not shown).

The number of women ever exposed to chloroform, carbon tetrachloride, motor gasoline, ethylene glycol and tetrahydrofuran was very low; for this reason, these five solvents were excluded from further analyses. Associations between head and neck cancer risk and other exposure variables are given in [table 3](#).

Chlorinated solvents

The risk of head and neck cancer increased with the duration of exposure to TCE ([table 3](#)). A similar increase in risk with duration of exposure was found for exposure to PCE. No clear relationship was observed between head and neck cancer and average intensity or cumulative exposure to TCE in the categorical analysis, the highest ORs being observed in the lowest cumulative exposure category. However, when average intensity and CEI were considered as continuous variables, significant trends were observed for both. On the other hand, for PCE, average intensity and cumulative exposure were not associated with head and neck cancer.

The distribution of job periods exposed to TCE by occupation (see online supplementary material figure 1) shows that the most frequently exposed occupations were shoes and leather workers, dry cleaners and launderers, rubber and plastics workers, welders and electronics workers. The most frequent sector of activity exposed to TCE was the leather and footwear industry.

Since leather workers may have also been exposed to benzene in the past, we also estimated mutually adjusted ORs for the association between head and neck cancer and exposure to TCE and benzene. The OR for TCE remained significantly elevated (OR=2.05, 95% CI 1.04 to 4.01) whereas no association with benzene exposure was found (OR=1.11, 95% CI 0.52 to 2.36).

The distribution of job periods exposed to PCE by occupation (see online supplementary material figure 2) shows that the most frequently exposed occupations were dry cleaners, launderers, degreasers and assemblers in electrical and electronic equipment. The most frequent sector of activity was laundry and dry cleaning.

Exposures to TCE and PCE were strongly correlated, and were also correlated to methylene chloride exposure, which makes the interpretation of mutually adjusted

Table 1 Main characteristics of cases and controls

	Cases		Controls		
	n	Per cent	n	Per cent	
Département					p=0.003
Calvados	23	7.8	104	13.4	
Doubs+Territoire de Belfort	1	0.3	31	4.0	
Hérault	44	14.9	90	11.6	
Isère	37	12.5	94	12.1	
Loire Atlantique	38	12.8	93	12.0	
Manche	37	12.5	65	8.4	
Bas-Rhin	33	11.2	109	14.1	
Haut-Rhin	9	3.0	29	3.7	
Somme	54	18.2	112	14.5	
Vendée	20	6.8	48	6.2	
Age at interview, years					p<0.0001
Mean (95% CI)	58.0 (56.9 to 59.0)		60.4 (59.6 to 61.2)		
Class (years)					
<50	51	17.2	160	20.6	
50–59.9	109	36.8	157	20.3	
60–69.9	99	33.4	246	31.8	
≥70	37	12.6	212	27.3	
Number of jobs held					p=0.01
Mean (95% CI)	3.3 (2.9 to 3.6)		3.7 (3.4 to 3.8)		
Range	18		13		
Socioeconomic status (the longest duration)					p=0.001
Farmers	3	1.1	29	3.8	
Self-employed workers	14	5.1	25	3.3	
Managers	19	6.9	74	9.7	
Intermediate white-collar workers	28	10.1	131	17.3	
Office and sales employees	150	54.1	375	49.4	
Blue-collar workers	63	22.7	125	16.5	
Missing	19	–	16	–	
Smoking					p<0.0001
Never*	60	20.3	509	66.1	
Former smokers†	46	15.5	134	17.4	
Current smokers	190	64.2	127	16.5	
Missing	–	–	5	–	
Pack-years (former and current)					p<0.0001
<6.89	23	9.9	100	38.5	
6.9–19.9	34	14.6	87	33.5	
20.0–35.24	78	33.5	47	18.1	
≥35.25	98	42.1	26	10.0	
Missing	3	–	6	–	
Drinking (drink-years)					p<0.0001
Never	44	15.4	177	22.9	
<2.79	39	13.6	173	22.4	
2.8–16.3	35	12.2	172	22.3	
16.4–64.9	51	17.8	155	20.0	
≥65.0	117	40.9	96	12.4	
Missing	10	–	2	–	

*Non-smokers were subjects who had smoked fewer than 100 cigarettes or equivalent in their lifetime.

†Former smokers were subjects who had stopped smoking at least 2 years before diagnosis (cases)/interview (controls).

ORs difficult. Instead, we studied exposure to exclusive combinations of chlorinated solvents (table 4). No case was exposed only to PCE. The OR associated with TCE alone was high (OR=1.81, 95% CI 0.81 to 4.04), but lower than in the analysis reported in table 2 (OR=2.15, 95% CI 1.21 to 3.81). Exposure to methylene chloride alone was associated with an OR lower than 1 (OR=0.50,

95% CI 0.11 to 2.18). A high OR was associated with joint exposure to TCE and PCE (OR=4.47, 95% CI 1.27 to 15.8).

Analyses by cancer sites are presented in table 5. The OR associated with TCE exposure was elevated for larynx (OR=3.80, 95%CI 1.55 to 9.32) and oral cavity (OR=2.12, 95%CI 0.97 to 4.60), the latter showing a

Table 2 Association between head and neck cancer and ever exposure to solvents

	Never exposed				Ever exposed				OR*	
	Cases		Controls		Cases		Controls			
	n	Per cent	n	Per cent	n	Per cent	n	Per cent		
Chloroform	272	98.2	748	98.7	5	1.8	10	1.3	0.36	0.09 to 1.49
Carbon tetrachloride	271	97.9	746	98.4	6	2.1	12	1.6	0.36	0.09 to 1.55
Methylene chloride	264	95.1	728	96.1	14	4.9	30	3.9	1.09	0.46 to 2.57
Trichloroethylene	240	86.6	697	92.2	38	13.4	60	7.8	2.15	1.21 to 3.81
Perchloroethylene	268	96.5	744	98.3	10	3.5	13	1.7	2.97	1.05 to 8.45
Motors gasoline	273	98.6	748	98.8	4	1.4	9	1.2	1.54	0.36 to 6.63
Special petroleum product	251	90.5	705	93	27	9.5	54	7.0	1.40	0.74 to 2.65
Diesel	264	95.1	731	96.6	14	4.9	26	3.4	1.79	0.75 to 4.29
Benzene	250	90.1	709	93.5	28	9.9	50	6.5	1.65	0.87 to 3.13
White-spirits	188	68.3	513	67.8	87	31.7	247	32.2	1.08	0.73 to 1.60
Ethylene glycol	276	99.6	752	99.3	1	0.4	5	0.7	1.75	0.17 to 18.4
Tetrahydrofuran	273	98.6	754	99.6	4	1.4	3	0.4	4.97	0.86 to 28.8
Diethyl ether	252	91.2	669	88.5	25	8.8	88	11.5	0.65	0.36 to 1.19
Ketones	234	84.5	675	89.2	44	15.5	83	10.8	1.61	0.96 to 2.70
Alcohols	152	55.6	394	52.4	123	44.4	364	47.6	0.83	0.57 to 1.20

*OR adjusted for age at interview, geographical area, alcohol and tobacco consumption.

dose–response relation with duration and cumulative exposure (see online supplementary material table SII; OR=6.84, 95% CI 2.11 to 22.1 for duration >10 years; OR=2.73, 95% CI 1.02 to 7.30 for CEI> median). There was also a suggestion of an increase in laryngeal cancer risk by duration of exposure. PCE exposure was associated with an increased risk of laryngeal (OR=7.95, 95% CI 1.92 to 32.9) and oropharyngeal cancers (OR=3.43, 95% CI 1.01 to 11.8). The small numbers of exposed cases made it difficult to study dose–response relationships.

Petroleum solvents

The study of the association between head and neck cancer and exposure to petroleum solvents (table 2) showed slight, non-significant elevations in risk for benzene (OR=1.65, 95% CI 0.87 to 3.13), diesel (OR=1.79, 95% CI 0.75 to 4.29) and special petroleum products (OR=1.40, 95% CI 0.74 to 2.65). No dose–response relationship was found with the duration of exposure, with the average intensity or with CEI (table 3). Exposure to white spirit (table 5) was associated with a non-significantly increased risk of oral cavity cancer (OR=1.54, 95% CI 0.90 to 2.66), which increased with CEI (OR=1.20, 95% CI 0.56 to 2.54 for CEI< median; OR=1.75, 95% CI 0.91 to 3.37 for CEI> median) and duration of exposure (OR=0.97, 95% CI 0.48 to 1.96 for <10 years; OR=2.51, 95% CI 1.25 to 5.02 for 10 years or more) (see online supplementary material table SIII).

Oxygenated solvents

With regard to oxygenated solvents (table 2), no elevated risks were associated with diethyl ether (OR=0.65, 95% CI 0.36 to 1.19) or alcohols (OR=0.83, 95% CI 0.57 to 1.20) exposure. An elevated but not significant OR (OR=1.61, 95% CI 0.96 to 2.70) was associated with

ketones exposure but without dose–response relationship with duration of exposure, average intensity or CEI (table 3). The OR associated with ever exposure to ketones was significantly elevated for laryngeal cancer (OR=2.66, 95% CI 1.17 to 6.07) but there was no increase in risk with duration of exposure or CEI (see online supplementary material table SIV).

DISCUSSION

We studied occupational exposures to chlorinated, petroleum and oxygenated solvents in relation to head and neck cancer risk in women in France. Some solvent exposures associated with an increased risk of cancer in women have been identified, notably exposure to TCE and PCE, with high and significant risks. For TCE, a clear and significant duration–response relationship was found and there was also some evidence of an increase in risk with intensity and cumulative exposure. For PCE, however, the increase in risk with duration was not significant and there was no indication of a dose–response relation with intensity or cumulative exposure. Risks associated with other solvents were sometimes slightly elevated but not significantly so, or without a duration–response relationship.

TCE is one of the most commonly used chlorinated solvents. It has been used as a metal degreasing product and was also widely used for manually degreasing textiles, or cleaning machinery and equipment when applying paints, glues, adhesives, plastics, rubbers and so on. TCE was recently classified as carcinogenic to humans (Group 1) based on sufficient epidemiological evidence for cancer of the kidney. Most of the information on the association between TCE and cancer risk derives from cohort studies which include only a small number of head and neck cancers, especially among women, and

Table 3 Association between head and neck cancer and exposure to selected solvents

	Never exposed	Duration of exposure												Mean intensity level						Cumulative Exposure Index												
		<10 years				≥10 years				Continuous				< Median			≥ Median			< Median			≥ Median			Continuous						
		OR*	95% CI	Ca	Co	OR*	95% CI	Ca	Co	OR*	95% CI	OR*	95% CI	Ca	Co	OR*	95% CI	Ca	Co	OR*	95% CI	OR*	95% CI	Ca	Co	OR*	95% CI	Ca	Co	OR*	95% CI	
Chlorinated solvents																																
Methylene chloride	1	Ref.	7	21	0.85	0.28 to 2.56	7	9	1.65	0.42 to 6.53	0.99	0.93 to 1.05	4	19	0.62	0.18 to 2.16	10	11	2.02	0.60 to 6.84	1.23	0.77 to 1.97	7	15	1.34	0.42 to 4.28	7	15	0.87	0.25 to 2.99	1.01	0.97 to 1.06
Trichloroethylene	1	Ref.	25	47	1.67	0.86 to 3.24	13	13	4.44	1.56 to 12.6	1.06	1.01 to 1.12	24	30	2.62	1.24 to 5.54	14	30	1.67	0.71 to 3.90	1.30	1.01 to 1.66	20	30	2.16	1.02 to 4.58	18	30	2.13	0.94 to 4.84	1.02	1.01 to 1.04
Perchloroethylene	1	Ref.	8	9	2.66	0.75 to 9.40	2	4	3.75	0.64 to 21.9	1.06	0.97 to 1.17	4	7	3.56	0.90 to 14.1	6	6	2.38	0.51 to 11.2	1.08	0.95 to 1.23	8	7	4.09	1.15 to 14.6	2	6	1.44	0.18 to 11.6	1.00	0.99 to 1.02
Petroleum solvents																																
Special petroleum product	1	Ref.	19	30	1.47	0.67 to 3.20	8	24	1.30	0.47 to 3.65	0.99	0.94 to 1.04	18	27	1.30	0.56 to 3.01	9	27	1.54	0.61 to 3.89	1.01	0.93 to 1.11	21	27	1.51	0.68 to 3.35	6	27	1.25	0.45 to 3.45	1.00	0.99 to 1.01
Diesel	1	Ref.	12	16	2.89	1.03 to 8.08	2	10	0.56	0.09 to 3.31	1.02	0.95 to 1.10	8	14	1.56	0.49 to 4.97	6	12	2.13	0.59 to 7.61	1.30	0.94 to 1.78	6	12	1.14	0.31 to 4.29	8	14	2.52	0.82 to 7.74	1.00	0.97 to 1.03
Benzene	1	Ref.	21	35	1.77	0.85 to 3.67	7	15	1.34	0.38 to 4.68	1.00	0.94 to 1.06	20	28	1.52	0.67 to 3.43	8	22	1.87	0.71 to 4.96	1.38	0.36 to 5.22	19	25	1.59	0.69 to 3.64	9	25	1.74	0.67 to 4.53	1.02	0.89 to 1.17
White spirits	1	Ref.	50	153	0.87	0.54 to 1.40	37	94	1.45	0.83 to 2.52	1.01	0.99 to 1.04	62	182	1.08	0.70 to 1.67	25	64	0.96	0.49 to 1.86	0.94	0.74 to 1.20	42	118	1.04	0.62 to 1.74	45	129	1.08	0.65 to 1.78	1.00	0.98 to 1.02
Oxygenated solvents																																
Diethyl ether	1	Ref.	9	25	1.07	0.39 to 2.91	16	63	0.52	0.25 to 1.07	0.98	0.95 to 1.01	12	44	0.58	0.25 to 1.33	13	44	0.73	0.32 to 1.67	0.01	0.00 to 326	13	44	0.89	0.41 to 1.95	12	44	0.46	0.19 to 1.10	0.70	0.41 to 1.27
Ketones	1	Ref.	32	55	1.71	0.94 to 3.11	12	28	1.42	0.58 to 3.48	1.02	0.98 to 1.06	22	42	1.68	0.81 to 3.46	22	41	1.56	0.79 to 3.06	1.11	0.92 to 1.35	28	42	2.27	1.16 to 4.44	16	41	1.10	0.52 to 2.31	1.01	0.99 to 1.02
Alcohols	1	Ref.	67	168	0.93	0.59 to 1.45	56	196	0.71	0.44 to 1.13	0.99	0.97 to 1.01	80	255	0.76	0.50 to 1.15	43	109	0.89	0.53 to 1.51	1.33	0.90 to 1.95	57	180	0.68	0.43 to 1.10	66	184	0.95	0.61 to 1.48	1.01	0.98 to 1.03

*OR adjusted for age at interview, geographical area, alcohol and tobacco consumption.
Ca, case; Co, control; Ref., women who have never been exposed to the current solvent are the reference category.

Table 4 Association between head and neck cancer and exclusive exposure to combinations of chlorinated solvents

	Cases (n=284)	Controls (n=767)	OR*	95% CI
Never exposed to TRI, PER or MC	246	693	1	
TRI only	20	32	1.81	0.81 to 4.04
PER only	0	3	–	–
TRI and PER	9	7	4.47	1.27 to 15.8
MC only	5	8	0.50	0.11 to 2.18
TRI and MC	8	18	1.66	0.58 to 4.77
TRI and PER and MC	1	3	2.16	0.19 to 24.1

*OR adjusted for age at interview, geographical area, alcohol and tobacco consumption. MC, methylene chloride; PER, perchloroethylene; TRI, trichloroethylene.

sometimes do not report results for these cancer sites. Wartenberg *et al*³⁴ reviewed data on exposure to TCE and cancer in a meta-analysis. They concluded that there was a weak suggestion of an increased risk of laryngeal cancer, and on average no evidence of an association with oral and pharyngeal cancer, despite substantial heterogeneity between studies. More recently, Raaschou-Nielsen³⁵ found Standardised Incidence Ratios (SIRs) of 1.8 for buccal cavity and pharynx cancers (10 observed) and 1.7 for larynx cancers (three observed) in women exposed to TCE in a Danish cohort study including more than 340 companies with documented use of TCE. Interestingly, the SIRs among men were lower, around 1.1 to 1.2. Boice *et al*³⁶ reported not significantly elevated Standardised Mortality Ratio (SMR) for buccal cavity and pharynx cancers (four observed) and for larynx cancers (two observed) among men exposed to TCE in a rocket engine testing facility. In 2013, Hansen *et al*³⁷ established a pooled cohort including 5553 workers with well-documented individual exposure to TCE in Finland, Sweden and Denmark. They observed an SIR for buccal and pharyngeal cancers of 1.71 (95% CI 0.74 to 3.38) and 2.94 (95% CI 0.36 to 10.6) respectively among men (eight observed) and among women (two observed). For laryngeal cancers, the SIR was 1.46 (95% CI 0.72 to 2.61) in men (11 observed) and no case was observed in women. In a cohort of aircraft maintenance workers,³⁸ a non-significantly increased risk of oral and pharyngeal cancer was observed for workers exposed versus not exposed to TCE among men (11 exposed cases, OR=1.23, 95% CI 0.34 to 4.43) and among women (two exposed cases, OR=1.08, 95% CI 0.18 to 6.47), but no gradient with cumulative exposure was apparent. Overall, several studies of workers exposed to TCE have reported elevated but not statistically significant relative risks for oral, pharyngeal and/or laryngeal cancer, but the small number of cases and the lack of data on confounding factors make interpretation difficult. Our finding of a significantly increased risk of head and neck cancer associated with TCE exposure, based on a case-control study with larger numbers of exposed cases and with thorough adjustment for alcohol and tobacco consumption is globally consistent with the literature. We also observed a duration-response relationship. Concerning cumulative exposure, our results are

less conclusive, with similar ORs below and above the median, but a globally significant trend with CEI. The increase in risk associated with TCE was larger for laryngeal cancer (OR=3.80, 95% CI 1.55 to 9.32), and somewhat smaller for cancer of the oral cavity (OR=2.12, 95% CI 0.97 to 4.60).

Since the 1950s, PCE, another widely used chlorinated solvent, was used extensively in dry cleaning, metal degreasing and for cleaning machinery and equipment. IARC classified PCE as 'probably carcinogenic to humans'.²⁵ Since the 1990s, its use has been more limited, particularly for metal degreasing, but it continues to be used for dry degreasing of clothes, albeit under stricter conditions. The literature on the risks of head and neck cancers related to exposure to PCE is very limited. Mundt *et al*³⁹ reviewed the risk of cancer linked to PCE exposure. They concluded that the possibility of an association between oral, pharyngeal and laryngeal cancer and PCE appeared unlikely. In a cohort of dry cleaners, a significantly elevated SMR was observed for laryngeal cancer among workers with the highest estimated level of exposure to dry cleaning solvents, primarily PCE.⁴⁰ Deaths from cancer of the buccal cavity and pharynx were not in excess in this cohort. In another cohort of dry cleaners, exposure to PCE was found to be associated with a significant increase in tongue cancer, but not in laryngeal cancer.⁴¹ As for TCE, these findings rely on small numbers of cases, and information on confounding factors was not available. A case-control study showed a high, although not significant, OR associated with exposure to PCE, after adjustment for alcohol and tobacco consumption.⁴² In another case-control study, in which smoking and alcohol drinking were controlled for, a significantly increased risk of laryngeal cancer was also found to be associated with exposure to chlorinated solvents, but information on specific solvents was not available.²⁴ In line with these results, we observed elevated ORs for laryngeal cancers in relation with PCE (four exposed cases, OR=7.95, 95% CI 1.92 to 32.9).

In our study, it is not possible to distinguish precisely the risks associated with TCE from those associated with PCE. Indeed, no woman in our study was exposed only to PCE. However, the study of combinations of exposures to different chlorinated solvents suggests that the risk for

Table 5 Association between head and neck cancer sites and ever exposure to selected solvents

Ever exposure to	Oral cavity			Oropharynx			Hypopharynx			Larynx		
	Controls	Cases	OR* CI 95%	Cases	OR* CI 95%	Cases	OR* CI 95%	Cases	OR* CI 95%	Cases	OR* CI 95%	
Methylene chloride	30	5	1.34 0.44 to 4.13	2	0.42 0.09 to 2.02	2	1.23 0.21 to 7.18	4	2.0 0.56 to 7.20			
Trichloroethylene	60	12	2.12 0.97 to 4.60	13	1.66 0.78 to 3.54	3	2.45 0.57 to 10.5	10	3.80 1.55 to 9.32			
Perchloroethylene	13	1	0.98 0.11 to 8.47	5	3.43 1.01 to 11.8	0	-	4	7.95 1.92 to 32.9			
Special petroleum product	54	10	1.79 0.78 to 4.09	7	0.87 0.35 to 2.17	2	1.05 0.19 to 5.78	7	2.24 0.82 to 6.09			
Diesel	26	2	0.88 0.18 to 4.32	5	1.90 0.60 to 6.03	2	3.60 0.55 to 23.4	4	2.51 0.66 to 9.53			
Benzene	50	9	1.79 0.76 to 4.22	9	1.39 0.58 to 3.31	2	0.97 0.17 to 5.43	6	2.07 0.72 to 5.97			
White spirits	247	32	1.54 0.90 to 2.66	21	0.54 0.30 to 0.95	10	1.67 0.65 to 4.29	20	1.70 0.86 to 3.37			
Diethyl ether	88	10	0.91 0.41 to 2.06	8	0.51 0.22 to 1.20	3	0.74 0.18 to 3.05	2	0.30 0.07 to 1.40			
Ketones	83	13	1.58 0.77 to 3.25	14	1.24 0.62 to 2.48	5	1.93 0.59 to 6.26	11	2.66 1.17 to 6.07			
Alcohols	365	41	1.02 0.61 to 1.73	40	0.59 0.36 to 0.97	15	1.43 0.57 to 3.56	22	0.89 0.46 to 1.75			

*OR adjusted for age at interview, geographical area, alcohol and tobacco consumption.

joint exposure to TCE and PCE (nine exposed cases, OR=4.47, 95% CI 1.27 to 15.8) is higher than for exposure to TCE only (20 exposed cases, OR=1.81, 95% CI 0.81 to 4.04).

Overall, our results are consistent with an effect of occupational exposure to these two chlorinated solvents on the occurrence of head and neck cancers, particularly with laryngeal cancer. Among men in the ICARE study,⁴³ there was also an increased risk of laryngeal cancer associated with high levels of exposure to PCE. However, no association was found between head and neck cancer and exposure to TCE in men, after adjustment for asbestos exposure. This difference in results between men and women is probably due to confounding by asbestos. In women, jobs involving exposure to TCE, mainly related to leather work or dry cleaning, are unlikely to entail exposure to asbestos, and actually adjusting for asbestos had no or very limited effect on the risk related to TCE in women. In men, the stronger correlation between asbestos and TCE exposure made it difficult to study an independent role of TCE. Another possible explanation is that there are true gender differences in risk. Some studies, although based on very small numbers, have suggested higher relative risks in women than in men, and gender differences in the toxicokinetics of TCE have been reported.^{28 29 44}

Petroleum solvents, and even more so oxygenated solvents, are also widely used by women in the workplace. Overall, our results do not provide evidence of a substantial role of these solvents in head and neck cancer aetiology. However, we found a significantly increased risk of cancer of the oral cavity among women exposed for more than 10 years to white spirits, as well as a significantly increased risk of laryngeal cancer associated with exposure to ketones. To the best of our knowledge, these associations have not been examined previously. Although these findings may be due to chance, they warrant further investigation.

One strength of our study is that it included almost 300 female incident cases of well-characterised squamous cell carcinomas of the head and neck (HNSCC). This makes it one of the largest case-control studies in women. The design of ICARE was population-based; cases were incident and were identified by qualified cancer registries in 10 French geographical areas. It was verified that the distribution of the main occupational and economic activity characteristics of the active population in these regions was similar to their distribution in France.³⁰ Participation rates were satisfactory for a population-based case-control study.³⁰ The control group was a random sample of the population of these areas and the distribution of socioeconomic characteristics was also similar to their distribution in the general population. Moreover, lifelong exposure prevalences among women controls were of the same order of magnitude as those estimated among women in the general population for the solvents under study.³³ Distribution by age, sex and cancer site of the head and neck cancer

cases included in ICARE was similar to that observed for head and neck cancer cases in all of France. Thus, selection bias is unlikely, and was probably marginal if it occurred at all.

Our study has some limitations. Despite a relatively large number of cases, statistical power was limited for in-depth analyses by cancer sites. As this is a case-control study, recall bias is possible. However, it should be very limited since the number of jobs reported by cases and controls was similar (on average 3.3 for cases and 3.7 for controls). Although occupations and industries are self-reported, it is unlikely that this bias would be differential between cases and controls because occupational exposures are not widely known to be risk factors for head and neck cancers, particularly among women. Coding occupation and industry is difficult and often not reproducible. However, coders received special training and were blind as to case-control status. If coding errors were made, they were therefore not differential. Residual confounding is always a possibility. But we took into account age, alcohol and tobacco consumption, the interaction between alcohol and tobacco, and socioeconomic status. Special attention was paid to adjustment for alcohol and tobacco consumption, with the use of cubic splines allowing to better account for the effect of these two confounding factors. Therefore, residual confounding in relation with alcohol and tobacco consumption is unlikely to be a major problem in this study. However, other known or suspected risk factors such as nutritional factors or human papilloma virus infection were not considered in this analysis but it is unlikely that they explain the observed associations.

Another limitation of our study is that this type of JEM analysis, based on job-specific averages, does not achieve a high level of accuracy in the exposure assessment.⁴⁵ The use of JEMs may produce misclassification of exposure, which is likely to be independent of case-control status. Non-differential misclassification bias results in an estimation of the OR biased towards 1, with an associated loss of statistical power for dichotomised exposures,⁴⁶ but may also distort exposure-response trends in multilevel exposure analyses.⁴⁷ In our categorical analyses for TCE and PCE, we found duration-response relationships, but no dose-response relation with intensity, and consequently no dose-response relation with cumulative exposure. Assessment of exposure levels is more prone to error than duration, so misclassification could partly explain our findings. Furthermore, the JEMs used are not gender specific. The construction of the JEMs³³ was based primarily on knowledge acquired from men, and misclassification may be more frequent among women. However, this type of bias cannot explain positive findings.

Finally, we assessed a large number of associations, and multiple comparisons may be an issue. Instead of applying an overly conservative adjustment, we chose to rely on the consistency of results between the different exposure variables, as well as on published results, to draw our conclusions.^{48 49}

CONCLUSION

In conclusion, our findings suggest that the exposure to TCE and PCE may increase the risk of HNSCC; in contrast, there is no clear evidence that the other solvents studied are risk factors for HNSCC. Nevertheless, further investigations are necessary to replicate these results in a larger, exposed female population.

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Contributors MC and DL designed the current study, conducted the analyses and drafted the manuscript; CB and GM contributed to the statistical analysis and interpretation of the results. DC, CP and BT were involved in data collection, management 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.

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