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Head and neck cancer and occupational exposure to solvents in women: results from the ICARE study

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Title

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Running title

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A Conflict of Interest Statement (a short statement either disclosing conflicts or declaring that no conflicts exist)

No conflicts exists

Contributors

MC and DL designed the current study, conducted the analyses and drafted the manuscript; CB, GM contributed to the statistical analysis and interpretation of the results. DC, CP, 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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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: 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 five chlorinated solvents (carbon tetrachloride; chloroform; methylene chloride; perchloroethylene; trichloroethylene), 5 petroleum solvents (benzene; special petroleum product; gasoline; white-spirits and other light aromatic mixtures; gasoil, fuels and kerosene) and 5 oxygenated solvents (alcohols; ketones and esters; ethylene glycol; diethyl ether; tetrahydrofuran). Odds ratio (ORs) and 95% confidence intervals (CI), adjusted for smoking, alcohol drinking, age and department, were estimated with logistic models.

Results: Elevated ORs were observed among women ever exposed to perchloroethylene (OR=2.97, 95%CI: 1.05-8.45) and trichloroethylene (OR=2.15, 95%CI: 1.21-3.81), which increased with exposure duration- (respectively OR=3.75, 95%CI: 0.64-21.9 and OR=4.44, 95%CI: 1.56-12.6 for ten years or more). 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 other studied solvents are risk factors for HNSCC.

Keywords: head and neck; cancer; trichloroethylene; perchloroethylene; occupational exposures; women; solvents

Strengths and limitations

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 nondifferential.

Despite a relatively large number of cases, statistical power was limited for in-depth analyses by cancer sites.

Data sharing statement: No additional data are available.

Introduction

Compared to other European Union countries, head and neck cancers (HNC) are frequent in France [1]. The world standardized cancer incidence rates in 2012 in France are greater than 16 per 100,000 for lip, oral cavity and pharynx (LOCP) cancers and 5.4 per 100,000 for laryngeal cancer in men, and greater than 5 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 HNC associated with exposure to solvents [23, 24]. Some solvents such as trichloroethylene [25], perchloroethylene [25] or benzene [26] are classified as proven or probable carcinogens by 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]. ICARE (Investigation of occupational and environmental CAuses of REspiratory cancers), 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 multi-center, 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 lip, oral cavity and pharynx (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 both head and neck cancer and lung cancer cases, and a distribution by socioeconomic status comparable to that of the general population. Subjects were interviewed face to face, using a standardized 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. 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 by the French Data Protection Authority (CNIL n° 90120).

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: i) oral cavity, 88 cases (29.7%): codes C00.3 – C00.9, C02.0 – C02.3, C03.0, C03.1, C03.9, C04.0, C04.1, C04.8, C04.9, C05.0, C06.0–C06.2, C06.8, and C06.9; ii) oropharynx, 111 cases (37.5%): codes C01.9, C02.4, C05.1, C05.2, C09.0, C09.1, C09.8, C09.9, C10.0–C10.4, C10.8, and C10.9; iii) hypopharynx, 28 cases (9.5%): codes C12.9, C13.0 – C13.2, C13.8, and C13.9; iv) oral cavity, pharynx unspecified or overlapping, 22 cases (7.4%): codes C02.8, C02.9, C05.8, C05.9, C14.0, C14.2, and C14.8; v) larynx, 47 cases (15.9%): codes C32.0 – C32.3 and C32.8 – C32.9. There were 296 cases and 775 controls in the final study group.

Coding of job titles

Each job held for at least one 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; perchloroethylene; trichloroethylene), 5 petroleum solvents (benzene; special petroleum product; gasoline; white-spirits and other light aromatic mixtures; gasoil, fuels and kerosene) and 5 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, JEM assigned three indices of exposure: (*i*) a probability of exposure expressed as the percentage of exposed workers (*ii*) an intensity of exposure and (*iii*) a frequency of exposure.

Probability of exposure was categorized into <1, 1–10, 11–20, 21–30, 31–40, 41–50, 51–60, 61–70, 71–80, 81–90, or up to 91–100% for chlorinated and oxygenated solvents and into <1, 1–10, 11–50, 50–90 or up to 91–100% for petroleum solvents.

Intensity of exposure was categorized into (*i*) <5, 5–25, 26–50, 51–100, >100 ppm for trichloroethylene, perchloroethylene, and methylene chloride; (*ii*) <0.1, 0.1–1, 1–5, 5–15, >15 ppm for benzene; (*iii*) <1, 1–20, 20–50, >50 ppm for white-spirits (WS); (*iv*) <1, 1–50, 50–150, >150 ppm for gasoline; (*v*) not exposed, very low, low, medium and high for carbon tetrachloride, chloroform, ketones and esters and alcohols; (*vi*) not exposed, low, medium and high for special petroleum product, gasoil-fuel and kerosene, ethylene glycol, tetrahydrofuran and diethyl ether.

Frequency of exposure was categorized into (*i*) <1, 1–10, 11–20, 21–30, 31–40, 41–50, 51–60, 61–70, 71–80, 81–90 or up to 91–100% of working time for chlorinated and oxygenated solvents; (*ii*) <0.5, 0.5–5, 5–30, 30–70, up to 71–100% of working time for petroleum solvents.

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

In all analyses, ‘never exposed’ refers to subjects never exposed to a specific solvent and was used as the reference category. ‘Ever exposed’ to a specific solvent refers to subjects having had at least one job with probability of exposure greater than zero. Cumulative duration of exposure was computed by summing all exposed periods and used as a continuous variable as well as a dichotomized, binary variable (cutpoint: 10 years).

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 the classes. The CEIs were used as continuous variables as well as transformed into binary variables according to the median of the distributions among controls.

Statistical analysis

Unconditional logistic regression was used to estimate odds ratios (ORs) and corresponding 95% confidence intervals (95% CI) of head and neck cancers. Analyses were adjusted for geographic 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 socioeconomic status (SES) assessed by the last occupation 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 odds ratios reported in the results section are those not adjusted for SES. Adjustment for asbestos exposure, was also performed; as was the case for SES, no significant effect was observed and these results are not presented here.

ORs were also estimated for each cancer site (as described upper: 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 I. On average, cases were 2 years younger than controls. This is explained by the fact that controls were stratified on age (in four categories: less than 40 years, 40-54 years, 55-64 years and >65 years) based on the age distribution of both head and neck cancer cases and lung cancer cases. The socioeconomic status of cases was lower than that of controls. Cases were less likely to be never smokers or never drinkers than controls.

Table II shows the association between head and neck cancers and ever exposed to chlorinated, petroleum and oxygenated solvents. The number of women ever exposed to chloroform (5 cases, 10 controls), carbon tetrachloride (6 cases, 12 controls), motors gasoline (4 cases, 9 controls), ethylene glycol (1 case, 5 controls) and tetrahydrofuran (4 cases, 3 controls) was very low; for this reason, these five solvents were excluded from further analyzes.

Ever exposure to trichloroethylene was associated with an increased risk of head and neck cancer (OR=2.15, 95% CI 1.21 to 3.81) and the risk increased with duration of exposure (OR=1.67, 95% CI 0.86 to 3.24 for less than 10 years and OR=4.44, 95% CI 1.56 to 12.6 for 10 years or more). Similar results were found for exposure to perchloroethylene, with an OR of 2.97 (95% CI 1.05 to 8.45) for ever exposure and an increase in risk with duration of exposure (OR=2.66, 95% CI 0.75 to 9.40 for less than 10 years and OR=3.75, 95% CI 0.64 to 21.9 for 10 years or more). On the other hand, no relationship was observed between head and neck cancer and cumulative exposure to trichloroethylene or perchloroethylene, the highest ORs being observed in the lowest cumulative exposure category. However, when duration or CEI was considered as a continuous variable, the relationship between head and neck cancer and CEI to trichloroethylene was significant (OR for elevation of 1 unit of CEI=1.02, 95% CI 1.01 to 1.04).

The study of the association between head and neck cancer and exposure to petroleum solvents showed slight, non significant elevations in risk for benzene (OR=1.65, 95% CI 0.87 to 3.13), gasoil (OR=1.79, 95% CI 0.75 to 4.29) and special petroleum product (OR=1.40, 95% CI 0.74 to 2.65). No dose-response relationship was found with the duration of exposure or with CEI.

With regards to oxygenated solvents, 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. A borderline significant elevated OR (OR=1.61, 95% CI 0.96 to 2.70) was associated with ketones exposure but without dose-response relationship with CEI (OR=2.27, 95% CI 1.16 to 4.44 for less than median and OR=1.10, 95% CI 0.52 to 2.31 for median or more) or duration of exposure.

The distribution of job periods exposed to trichloroethylene by occupation (See Supplementary material: Figure 1) shows that the most frequent 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 trichloroethylene was the leather and footwear industry.

Since leather workers are also exposed to benzene, we also estimated mutually adjusted ORs for the association between head and neck cancer and exposure to trichloroethylene and benzene. The OR for trichloroethylene 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 perchloroethylene by occupation (See Supplementary material: Figure 2) shows that the most frequent occupations were dry cleaners launderers, degreasers, assemblers in electrical and electronic equipment. The most frequent sector of activity was laundry and dry cleaning.

Exposures to trichloroethylene and perchloroethylene were strongly correlated, and were also correlated to methylene chloride exposure, which makes the interpretation of mutually adjusted ORs difficult. Instead, we studied exposure to exclusive combinations of chlorinated solvents (Table III). No cases were exposed only to perchloroethylene. The odds ratio associated with trichloroethylene alone is high (OR=1.81, 95% CI 0.81 to 4.04), but lower than in the analysis reported in Table II (OR=2.15, 95% CI 1.21 to 3.81). Exposure to methylene chloride alone is associated with an OR lower than 1 (OR=0.50, 95% CI 0.11 to 2.18). A high OR was associated with the joint exposure to trichloroethylene and perchloroethylene (OR=4.47, 95% CI 1.27 to 15.8).

Analyses by cancer sites are presented in Table IV. The OR associated with trichloroethylene exposure was higher 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 dose-response relation with duration and cumulative exposure (See Supplementary material: Table S-I, 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). Perchloroethylene 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), with no clear indication of dose-response relationships. 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 Supplementary materiel: Table S-III). Exposure to white-spirit (See Supplementary materiel: Table S-II) 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).

Discussion

This analysis 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. This is the case for exposure to trichloroethylene or perchloroethylene, with high and significant risks and with a duration-response relationship. Risks associated with other solvents were sometimes slightly elevated but not significantly so, or without duration-response relationships.

Trichloroethylene (TCE) is one of the most 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 while applying paints, glues, adhesives, plastics, rubbers, etc. 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 sometimes do not report results for these cancer sites. Wartenberg et coll [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-Nielsen [35] found SIRs of 1.8 for buccal cavity and pharynx cancers (10 observed) and 1.7 for larynx cancers (3 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 coll. [36] reported a SMR of 1.25 for buccal cavity and pharynx cancers (4 observed) and 1.45 for larynx cancers (2 observed) among men exposed to TCE in a rocket engine testing facility. In 2013, Hansen et coll. [37] established a pooled cohort including 5553 workers with well documented individual exposure to TCE in Finland, Sweden and Denmark. They observed a SIR of 1.71 (95% CI 0.74 to 3.38) and 2.94 (95% CI 0.36 to 10.6) for buccal and pharyngeal cancers among men (8 observed) and women (2 observed) respectively. For laryngeal cancers, 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 vs not exposed to TCE among men (11 exposed cases, OR=1.23, 95% CI 0.34 to 4.43) and among women (2 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 higher for laryngeal cancer (OR=3.80, 95% CI 1.55 to 9.32), and to a lesser extent for cancer of the oral cavity (OR=2.12, 95% CI 0.97 to 4.60). However, a clear dose-response gradient with duration and cumulative exposure was apparent for oral cancer (OR 1.16 to 6.84 for less vs more than 10 years of exposure and 1.38 to 2.73 for less vs more than the median CEI), whereas similarly high ORs were observed in all categories of duration and cumulative exposure for laryngeal cancer.

Since the 1950s, perchloroethylene (PCE), another widely used chlorinated solvent, was used extensively in dry cleaning but also for metal degreasing and for cleaning machinery and equipment. IARC classified PCE as *probably carcinogenic to humans* [25]. Since the 1990's, its use has been more limited, particularly for metal degreasing, but it remains effective 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 coll. [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 with 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 (4 exposed cases, OR=7.95, 95% CI 1.92 to 32.9). However, we did not find any dose-response relationship, the highest ORs being observed in the lowest duration and CEI categories.

In our study, it is not possible to distinguish precisely the risks associated to TCE and to PCE. Indeed, none of these women was exposed only to PCE. However, the study of combinations of exposures to different chlorinated solvents suggests that the risk for joint exposure to TCE and PCE (9 exposed cases, OR=4.47, 95% CI 1.27 to 15.8) is higher than for exposure to only TCE (20 exposed cases, OR=1.81, 95% CI 0.81 to 4.04).

In all, 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 etiology. 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 our knowledge, these associations have not be 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 characterized 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 on the same order of magnitude to that 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. Since 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 in 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, 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 HPV infection were not considered in this analysis but it is unlikely that they explain the risks identified.

Another possible limitation of our study is that this type of JEM-analysis, based on job-specific averages, do not achieve a high level of accuracy in the exposure assessment [45]. This procedure can produce misclassifications resulting in an estimation of the odds ratio biased towards 1, with an associated loss of statistical power [46]. However, this type of bias cannot explain positive findings.

Conclusion

In conclusion, our findings suggest that the exposure to TCE and PCE may be a risk factor for HNSCC in women; 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.

Acknowledgements

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Table I: Main characteristics of cases and controls

	Cases		Controls	
	n	%	n	%
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 (56.9-59.0)		60.4 (59.6-61.2)	
Class				
<50 years	51	17.2	160	20.6
50-59.9 years	109	36.8	157	20.3
60-69.9 years	99	33.4	246	31.8
≥ 70 years	37	12.6	212	27.3
Number of jobs held				p=0.01
Mean (95%CI)	3.3 (2.9-3.6)		3.7 (3.4-3.8)	
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	-

*: Nonsmokers 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).

Table II: Association between head and neck cancer and exposure to selected solvents

	Never Exposed				Ever exposed				Cumulative Exposure Index										Duration of exposure									
									< median				≥ median				Continuous		< 10 years				≥ 10 years				Continuous	
	Ca	Co	OR#	95% CI	Ca	Co	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
Chlorinated solvents																												
Methylene chloride	264	728	1	Ref.	14	30	1.09	0.46 to 2.57	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	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
Trichloroethylene	240	697	1	Ref.	38	60	**2.15****	**1.21 to 3.81**	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**	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**
Perchloroethylene	268	744	1	Ref.	10	13	**2.97***	**1.05 to 8.45**	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	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
Petroleum solvents																												
Special petroleum product	251	705	1	Ref.	27	54	1.40	0.74 to 2.65	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	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
Gasoil	264	731	1	Ref.	14	26	1.79	0.75 to 4.29	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	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
Benzene	250	709	1	Ref.	28	50	1.65	0.87 to 3.13	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	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
White-spirits	188	513	1	Ref.	87	247	1.08	0.73 to 1.60	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	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
Oxygenated solvents																												
Diethyl ether	252	669	1	Ref.	25	88	0.65	0.36 to 1.19	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	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
Ketones	234	675	1	Ref.	44	83	1.61	0.96 to 2.70	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	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
Alcohols	152	394	1	Ref.	123	364	0.83	0.57 to 1.20	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	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

OR adjusted for age at interview, department, alcohol and tobacco consumption.
* p<0.05
** p<0.01

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

	Cases (n=284)	Controls (n=767)	OR#	95% CI	P
Never exposed to TRI, PER or MC	246	693	1		
TRI only	20	32	1.81	0,81 to 4,04	0.15
PER only	0	3	-	-	
TRI and PER	9	7	**4.47**	**1,27 to 15,8**	**0.02**
MC only	5	8	0.50	0,11 to 2,18	0.35
TRI and MC	8	18	1.66	0,58 to 4,77	0.34
TRI and PER and MC	1	3	2.16	0,19 to 24,1	0.53

TRI: trichloroethylene, PER: perchloroethylene, MC: methylene chloride

OR adjusted for age at interview, department, alcohol and tobacco consumption.

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

		Oral cavity				Oropharynx				Hypopharynx				Larynx			
Ever exposure to	**Controls**	**Cases**	**OR#**	**CI 95%**	**p**	**Cases**	**OR#**	**CI 95%**	**p**	**Cases**	**OR#**	**CI 95%**	**p**	**Cases**	**OR#**	**CI 95%**	**p**
Methylene chloride	30	5	1.34	0.44 to 4.13	0.60	2	0.42	0.09 to 2.02	0.28	2	1.23	0.21 to 7.18	0.81	4	2.0	0.56 to 7.20	0.28
Trichloroethylene	60	12	2.12	0.97 to 4.60	0.06	13	1.66	0.78 to 3.54	0.18	3	2.45	0.57 to 10.5	0.22	**10**	**3.80****	**1.55 to 9.32**	**0.003**
Perchloroethylene	13	1	0.98	0.11 to 8.47	0.98	**5**	**3.43***	**1.01 to 11.8**	**0.05**	0	-	-	-	**4**	**7.95****	**1.92 to 32.9**	**0.004**
Special petroleum product	54	10	1.79	0.78 to 4.09	0.17	7	0.87	0.35 to 2.17	0.76	2	1.05	0.19 to 5.78	0.95	**7**	2.24	0.82 to 6.09	0.11
Gasoil	26	2	0.88	0.18 to 4.32	0.87	5	1.90	0.60 to 6.03	0.27	2	3.60	0.55 to 23.4	0.18	4	2.51	0.66 to 9.53	0.17
Benzene	50	9	1.79	0.76 to 4.22	0.18	9	1.39	0.58 to 3.31	0.45	2	0.97	0.17 to 5.43	0.97	6	2.07	0.72 to 5.97	0.17
White-spirits	247	32	1.54	0.90 to 2.66	0.12	**21**	**0.54***	**0.30 to 0.95**	**0.03**	10	1.67	0.65 to 4.29	0.28	20	1.70	0.86 to 3.37	0.12
Diethyl ether	88	10	0.91	0.41 to 2.06	0.83	8	0.51	0.22 to 1.20	0.12	3	0.74	0.18 to 3.05	0.67	2	0.30	0.07 to 1.40	0.12
Ketones	83	13	1.58	0.77 to 3.25	0.22	14	1.24	0.62 to 2.48	0.54	5	1.93	0.59 to 6.26	0.27	**11**	**2.66***	**1.17 to 6.07**	**0.02**
Alcohols	365	41	1.02	0.61 to 1.73	0.93	**40**	**0.59***	**0.36 to 0.97**	**0.03**	15	1.43	0.57 to 3.56	0.44	22	0.89	0.46 to 1.75	0.74

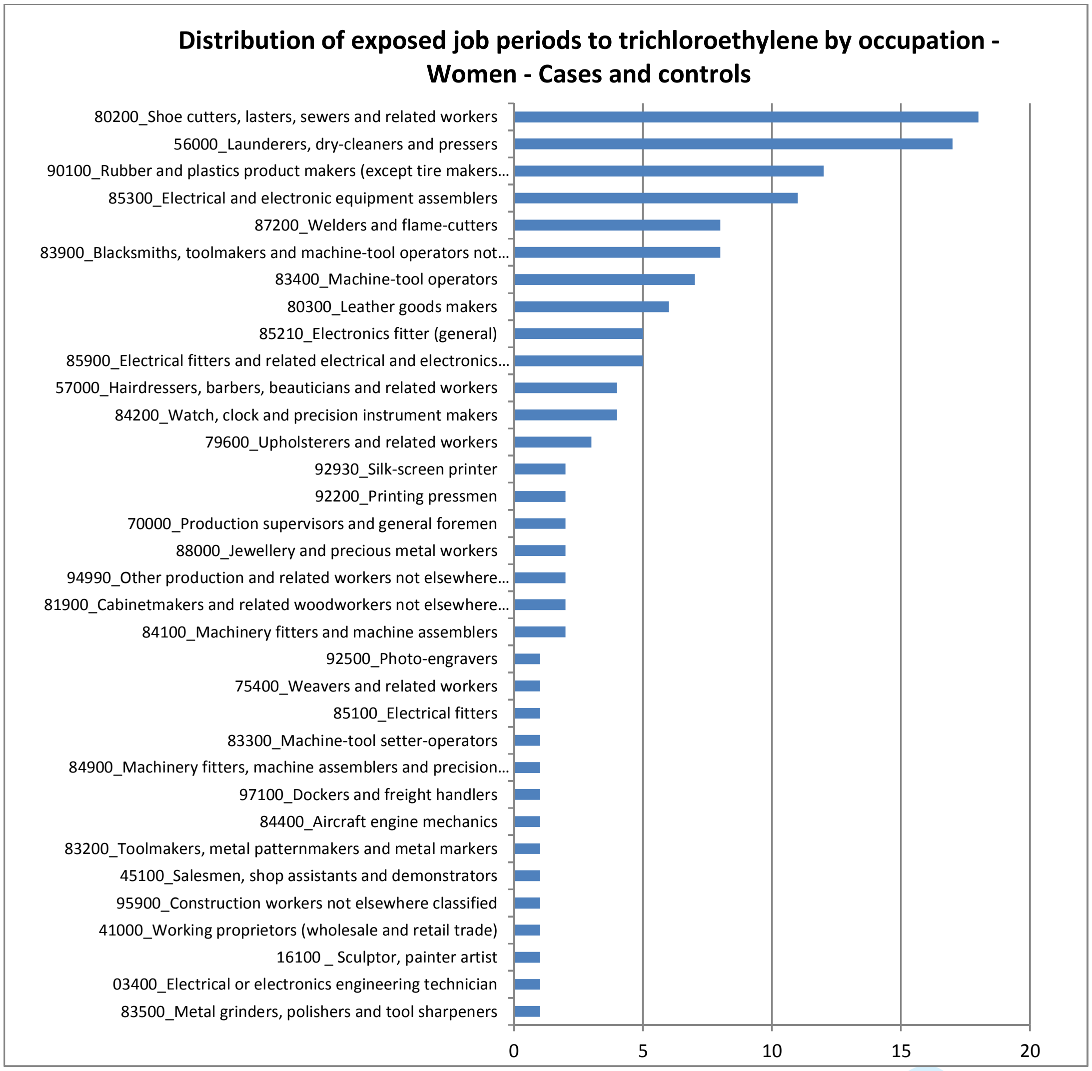
OR adjusted for age at interview, department, alcohol and tobacco consumption.

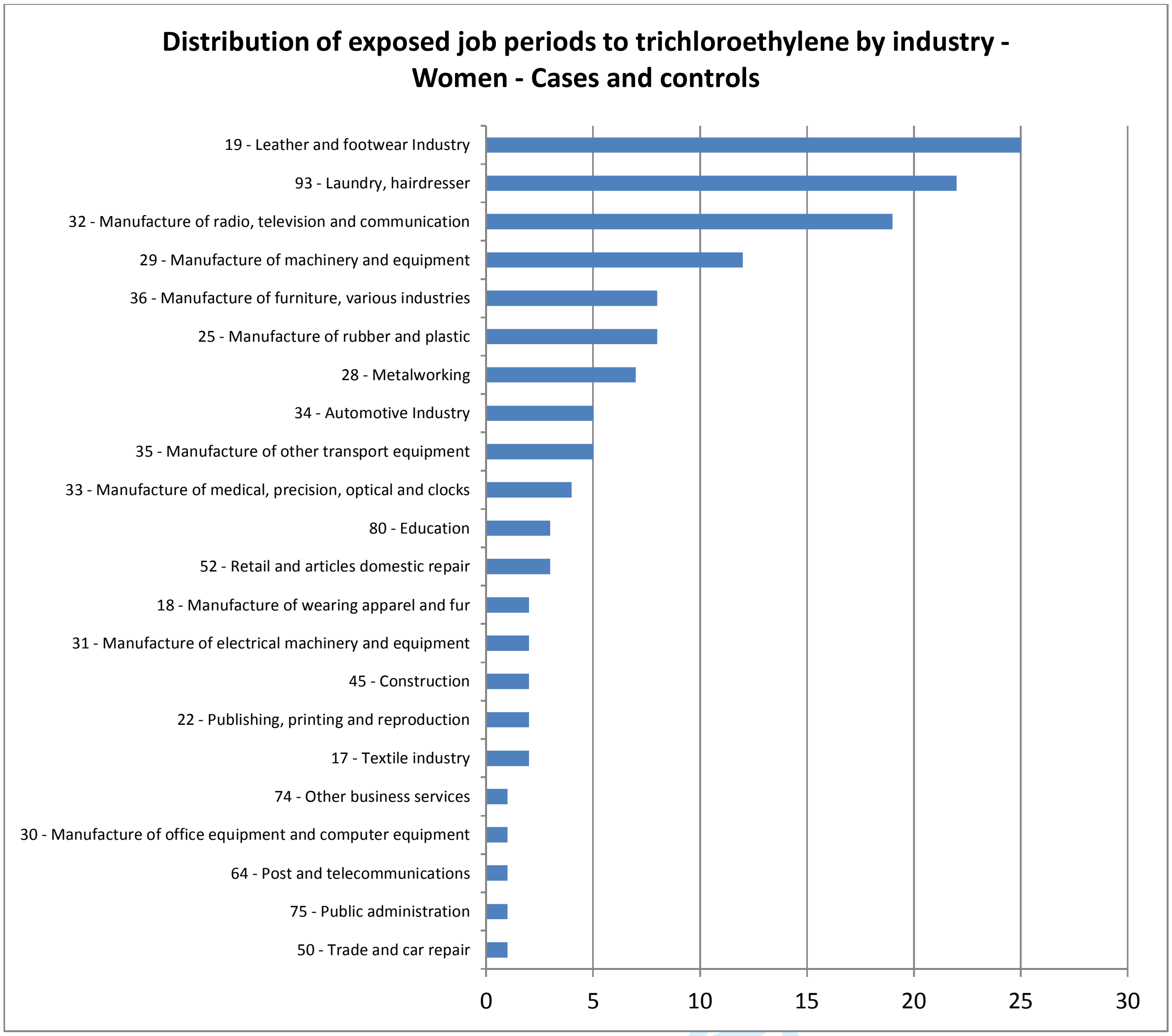
* p<0.05

** p<0.01

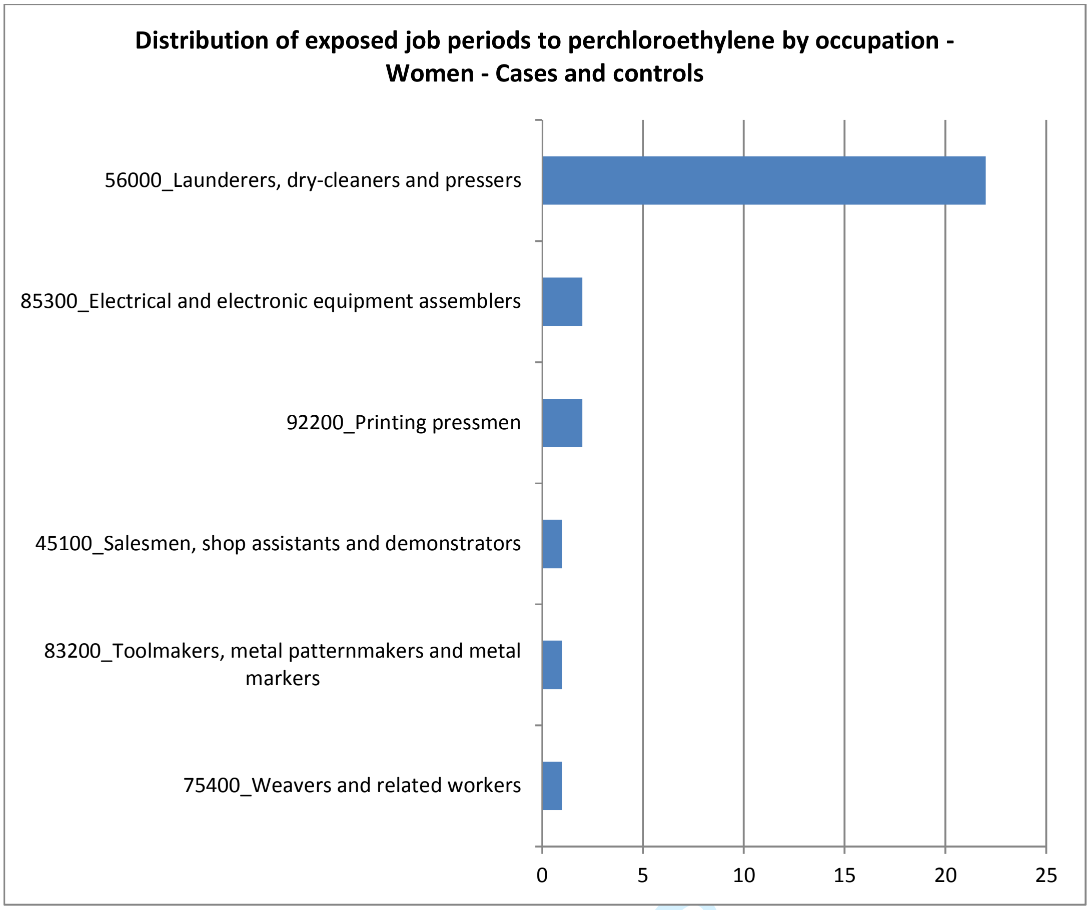
SUPPLEMENTARY MATERIALS

Supplementary - Figures 1




Distribution of exposed job periods to trichloroethylene by industry - Women - Cases and controls
19 - Leather and footwear Industry
93 - Laundry, hairdresser
32 - Manufacture of radio, television and communication
29 - Manufacture of machinery and equipment
36 - Manufacture of furniture, various industries
25 - Manufacture of rubber and plastic
28 - Metalworking
34 - Automotive Industry
35 - Manufacture of other transport equipment
33 - Manufacture of medical, precision, optical and clocks
80 - Education
52 - Retail and articles domestic repair
18 - Manufacture of wearing apparel and fur
31 - Manufacture of electrical machinery and equipment
45 - Construction
22 - Publishing, printing and reproduction
17 - Textile industry
74 - Other business services
30 - Manufacture of office equipment and computer equipment
64 - Post and telecommunications
75 - Public administration
50 - Trade and car repair
0
5
10
15
20
25
30

Supplementary - Figures 2



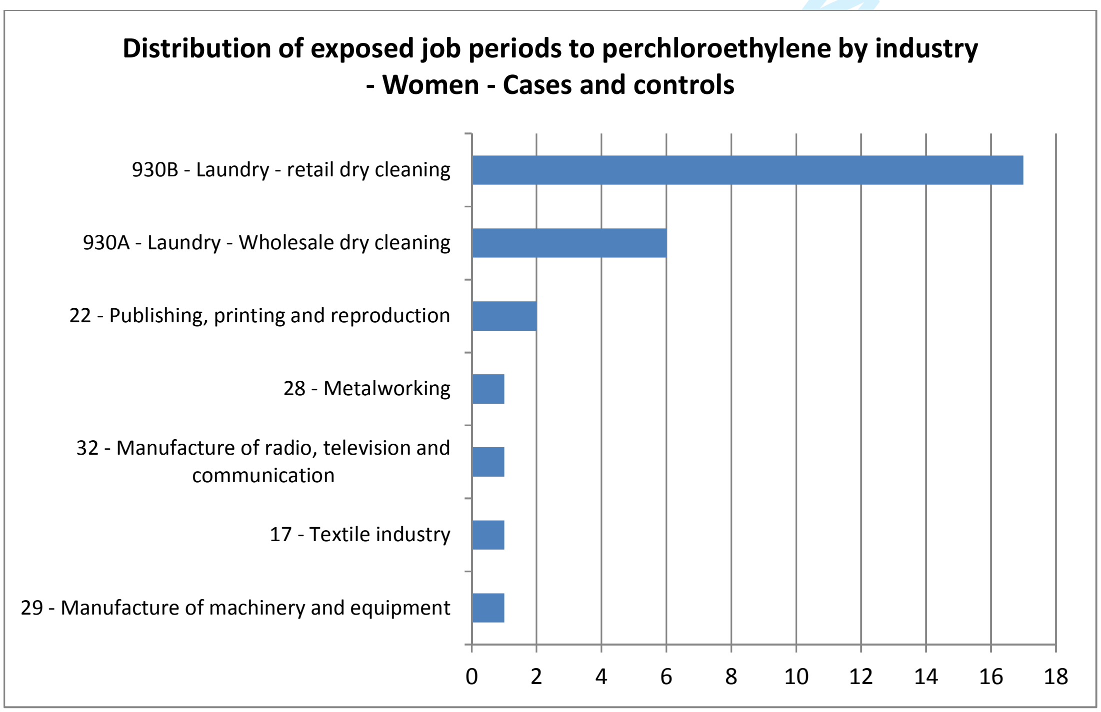


Table S-I: Association between head and neck cancer site and exposure to chlorinated solvents

		Oral cavity				Oropharynx				Hypopharynx				Larynx			
	Controls	Cases	OR#	CI 95%	p	Cases	OR#	CI 95%	p	Cases	OR#	CI 95%	p	Cases	OR#	CI 95%	p
Methylene chloride																	
Ever exposed	30	5	1.34	0.44 to 4.13	0.60	2	0.42	0.09 to 2.02	0.28	2	1.23	0.21 to 7.18	0.81	4	2.0	0.56 to 7.20	0.28
Cumulative Exposure Index																	
< median	15	2	1.39	0.27 to 7.16	0.69	2	0.92	0.17 to 4.94	0.92	-	-	-	-	3	3.12	0.65 to 14.9	0.15
≥ median	15	3	1.30	0.29 to 5.90	0.73	-	-	-	-	2	1.78	0.24 to 13.5	0.57	1	0.95	0.10 to 9.29	0.96
Duration of exposure																	
< 10 years	21	2	0.79	0.16 to 4.05	0.78	1	0.32	0.04 to 2.75	0.30	1	1.11	0.10 to 12.0	0.93	3	2.35	0.54 to 10.3	0.25
≥ 10 years	9	3	2.52	0.52 to 12.3	0.25	1	0.64	0.06 to 6.36	0.70	1	1.53	0.12 to 19.6	0.74	1	1.52	0.14 to 16.7	0.73
Trichloroethylene																	
Ever exposed	60	12	2.12	0.97 to 4.60	0.058	13	1.66	0.78 to 3.54	0.18	3	2.45	0.57 to 10.5	0.22	**10**	**3.80****	**1.55 to 9.32**	**0.003**
Cumulative Exposure Index																	
< median	30	4	1.38	0.42 to 4.57	0.59	9	2.30	0.93 to 5.71	0.07	1	1.22	0.12 to 12.1	0.86	**6**	**4.22***	**1.34 to 13.3**	**0.013**
≥ median	30	**8**	**2.73***	**1.02 to 7.30**	0.04	4	0.97	0.27 to 3.42	0.96	2	4.13	0.72 to 23.7	0.11	4	3.25	0.92 to 11.4	0.067
Duration of exposure																	
< 10 years	47	6	1.16	0.42 to 3.22	0.78	9	1.48	0.62 to 3.49	0.37	3	2.31	0.52 to 10.3	0.27	**8**	**3.47***	**1.28 to 9.41**	**0.014**
≥ 10 years	13	**6**	**6.84****	**2.11 to 22.1**	0.001	4	2.54	0.63 to 10.3	0.19	0	-	-	-	2	4.73	0.86 to 26.0	0.074
Perchloroethylene																	
Ever exposed	13	1	0.98	0.11 to 8.47	0.98	**5**	**3.43***	**1.01 to 11.8**	**0.05**	0	-	-	-	**4**	**7.95****	**1.92 to 32.9**	**0.004**
Cumulative Exposure Index																	
< median	7	1	1.59	0.17 to 14.7	0.68	3	3.76	0.75 to 18.9	0.11	0	-	-	-	**4**	**15.8*****	**3.19 to 77.8**	**0.0007**
≥ median	6	0	-	-	0.99	2	2.59	0.32 to 20.7	0.36	0	-	-	-	0	-	-	-
Duration of exposure																	
< 10 years	9	0	-	-	0.99	4	3.55	0.80 to 15.7	0.09	0	-	-	-	**4**	**9.96****	**2.04 to 48.5**	**0.004**
≥ 10 years	4	1	9.50	0.89 to 101	0.06	1	3.22	0.33 to 31.5	0.31	0	-	-	-	0	-	-	-

OR adjusted for age at interview, department, alcohol and tobacco consumption.

* p<0.05

** p<0.01

Table S-II: Association between head and neck cancer site and exposure to petroleum solvents

		Oral cavity				Oropharynx				Hypopharynx				Larynx			
	Controls	**Cases**	**OR#**	**CI 95%**	**p**	**Cases**	**OR#**	**CI 95%**	**p**	**Cases**	**OR#**	**CI 95%**	**p**	**Cases**	**OR#**	**CI 95%**	**p**
Special petroleum product																	
Ever exposed	54	10	1.79	0.78 to 4.09	0.17	7	0.87	0.35 to 2.17	0.76	2	1.05	0.19 to 5.78	0.95	**7**	2.24	0.82 to 6.09	0.11
Cumulative Exposure Index																	
< median	27	7	1.86	0.66 to 5.25	0.24	5	0.86	0.28 to 2.63	0.79	2	1.43	0.24 to 8.63	0.69	**7**	**3.12***	**1.04 to 9.33**	**0.042**
≥ median	27	3	1.81	0.50 to 6.59	0.37	2	0.96	0.20 to 4.57	0.95	0	-	-	-	0	-	-	-
Duration of exposure																	
< 10 years	30	5	1.30	0.43 to 3.97	0.64	6	1.12	0.39 to 3.18	0.83	1	0.79	0.08 to 7.41	0.83	**7**	**3.31***	**1.12 to 9.74**	**0.030**
≥ 10 years	24	5	2.75	0.85 to 8.85	0.091	1	0.39	0.05 to 3.19	0.38	1	1.55	0.13 to 19.0	0.73	0	-	-	-
Gasoil																	
Ever exposed	26	2	0.88	0.18 to 4.32	0.87	5	1.90	0.60 to 6.03	0.27	2	3.60	0.55 to 23.4	0.18	4	2.51	0.66 to 9.53	0.17
Cumulative Exposure Index																	
< median	12	0	-	-	0.99	3	1.81	0.38 to 8.53	0.45	1	3.24	0.24 to 44.3	0.37	2	1.62	0.25 to 10.6	0.61
≥ median	14	2	1.91	0.37 to 9.78	0.44	2	1.80	0.33 to 9.88	0.49	1	3.57	0.27 to 47.1	0.33	2	3.60	0.62 to 20.7	0.15
Duration of exposure																	
< 10 years	16	2	1.62	0.30 to 8.65	0.57	4	3.02	0.80 to 11.5	0.10	1	3.38	0.28 to 41.1	0.33	**4**	**4.42***	**1.04 to 18.8**	**0.045**
≥ 10 years	10	0	-	-	0.99	1	0.62	0.06 to 6.36	0.68	1	4.87	0.33 to 71.7	0.24	0	-	-	-
Benzene																	
Ever exposed	50	9	1.79	0.76 to 4.22	0.18	9	1.39	0.58 to 3.31	0.45	2	0.97	0.17 to 5.43	0.97	6	2.07	0.72 to 5.97	0.17
Cumulative Exposure Index																	
< median	25	6	1.86	0.63 to 5.52	0.26	6	1.17	0.40 to 3.43	0.77	1	0.78	0.08 to 7.72	0.82	5	2.57	0.75 to 8.79	0.13
≥ median	25	3	1.62	0.42 to 6.22	0.48	3	2.06	0.53 to 8.01	0.29	1	1.21	0.10 to 14.8	0.88	1	0.90	0.09 to 8.79	0.92
Duration of exposure																	
< 10 years	35	5	1.47	0.51 to 4.29	0.48	8	1.72	0.67 to 4.42	0.25	1	0.87	0.09 to 8.12	0.90	6	**3.03***	**1.02 to 9.18**	**0.050**
≥ 10 years	15	4	2.32	0.57 to 9.48	0.24	1	0.56	0.06 to 5.07	0.60	1	0.93	0.06 to 13.6	0.95	0	-	-	-
White-spirits																	
Ever exposed	247	32	1.54	0.90 to 2.66	0.12	**21**	**0.54***	**0.30 to 0.95**	**0.03**	10	1.67	0.65 to 4.29	0.28	20	1.70	0.86 to 3.37	0.12
Cumulative Exposure Index																	
< median	117	12	1.20	0.56 to 2.54	0.64	10	0.53	0.25 to 1.15	0.10	8	2.75	0.91 to 8.32	0.074	10	1.76	0.75 to 4.17	0.19
≥ median	129	20	1.75	0.91 to 3.37	0.09	11	0.51	0.23 to 1.09	0.08	2	0.52	0.10 to 2.71	0.43	10	1.70	0.71 to 4.06	0.23
Duration of exposure																	
< 10 years	152	14	0.97	0.48 to 1.96	0.93	**11**	**0.41***	**0.20 to 0.85**	**0.02**	9	2.02	0.70 to 5.84	0.19	14	1.68	0.77 to 3.64	0.19
≥ 10 years	94	**18**	**2.51****	**1.25 to 5.02**	**0.009**	10	0.75	0.33 to 1.69	0.48	1	0.47	0.05 to 4.23	0.50	6	1.73	0.62 to 4.83	0.29

OR adjusted for age at interview, department, alcohol and tobacco consumption.

* p<0.05

** p<0.01

Table S-III: Association between head and neck cancer site and exposure to oxygenated solvents

		Oral cavity				Oropharynx				Hypopharynx				Larynx			
	Controls	Cases	OR#	CI 95%	p	Cases	OR#	CI 95%	p	Cases	OR#	CI 95%	p	Cases	OR#	CI 95%	p
Diethyl ether																	
Ever exposed	88	10	0.91	0.41 to 2.06	0.83	8	0.51	0.22 to 1.20	0.12	3	0.74	0.18 to 3.05	0.67	2	0.30	0.07 to 1.40	0.12
Cumulative Exposure Index																	
< median	44	6	1.57	0.56 to 4.42	0.39	3	0.47	0.13 to 1.69	0.24	1	0.64	0.07 to 5.82	0.69	1	0.43	0.05 to 3.46	0.42
≥ median	44	4	0.51	0.15 to 1.74	0.28	5	0.51	0.17 to 1.56	0.24	2	0.73	0.12 to 4.58	0.74	1	0.21	0.03 to 1.86	0.16
Duration of exposure																	
< 10 years	25	4	1.49	0.42 to 5.35	0.54	2	0.64	0.13 to 3.09	0.57	1	0.98	0.10 to 9.76	0.98	1	0.77	0.09 to 6.62	0.81
≥ 10 years	63	6	0.71	0.26 to 1.95	0.50	6	0.46	0.18 to 1.24	0.12	2	0.65	0.12 to 3.64	0.62	1	0.18	0.02 to 1.48	0.11
Ketones																	
Ever exposed	83	13	1.58	0.77 to 3.25	0.22	14	1.24	0.62 to 2.48	0.54	5	1.93	0.59 to 6.26	0.27	**11**	**2.66***	**1.17 to 6.07**	**0.020**
Cumulative Exposure Index																	
< median	42	8	2.08	0.83 to 5.23	0.13	10	1.94	0.82 to 4.58	0.12	**4**	**4.37***	**1.13 to 16.9**	**0.032**	**7**	**3.46***	**1.24 to 9.65**	**0.018**
≥ median	41	5	1.17	0.40 to 3.42	0.77	4	0.65	0.21 to 2.07	0.47	1	0.51	0.05 to 4.87	0.55	4	2.04	0.60 to 6.98	0.25
Duration of exposure																	
< 10 years	55	8	1.35	0.56 to 3.26	0.50	11	1.43	0.65 to 3.15	0.38	3	1.70	0.42 to 6.95	0.45	**10**	**3.34****	**1.38 to 8.10**	**0.008**
≥ 10 years	28	5	2.19	0.70 to 6.81	0.18	3	0.85	0.23 to 3.20	0.81	2	2.46	0.37 to 16.4	0.35	1	0.93	0.11 to 7.99	0.95
Alcohols																	
Ever exposed	365	41	1.02	0.61 to 1.73	0.93	**40**	**0.59***	**0.36 to 0.97**	**0.03**	15	1.43	0.57 to 3.56	0.44	22	0.89	0.46 to 1.75	0.74
Cumulative Exposure Index																	
< median	180	17	0.80	0.41 to 1.58	0.52	**18**	**0.48***	**0.25 to 0.91**	**0.02**	11	1.86	0.67 to 5.16	0.23	11	0.77	0.34 to 1.77	0.54
≥ median	184	24	1.22	0.66 to 2.27	0.53	22	0.68	0.37 to 1.25	0.21	4	0.73	0.20 to 2.70	0.63	11	1.03	0.45 to 2.37	0.93
Duration of exposure																	
< 10 years	168	20	1.05	0.55 to 2.01	0.87	20	0.62	0.34 to 1.15	0.12	10	1.91	0.68 to 5.38	0.22	15	1.24	0.58 to 2.64	0.58
≥ 10 years	196	21	0.96	0.51 to 1.83	0.90	20	0.54	0.29 to 1.01	0.055	5	0.82	0.23 to 2.87	0.75	7	0.57	0.22 to 1.46	0.24

OR adjusted for age at interview, department, alcohol and tobacco consumption.

* p<0.05

** p<0.01

STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation	Page in main doc
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	7-8
		(*b*) For matched studies, give matching criteria and the number of controls per case	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10-11
		(*b*) Describe any methods used to examine subgroups and interactions	10-11
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how matching of cases and controls was addressed	
		(*e*) Describe any sensitivity analyses	11
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	X
		(b) Give reasons for non-participation at each stage	X
		(c) Consider use of a flow diagram	X
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12 + Table I
		(b) Indicate number of participants with missing data for each variable of interest	12 + Table I
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	Table II
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates	12-14 +

	and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	**Tables**
	(*b*) Report category boundaries when continuous variables were categorized	**Tables**
	(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	**14 + Tables and Suppl. Mat**
Discussion			
Key results	18	Summarise key results with reference to study objectives	**16**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	**20-21**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	**16-19**
Generalisability	21	Discuss the generalisability (external validity) of the study results	**22**
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	**23**

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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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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Title

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

Running title

Head and neck cancer and occupational exposure to solvents in women

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A Conflict of Interest Statement (a short statement either disclosing conflicts or declaring that no conflicts exist)

The authors declare no conflict of interest

Contributors

MC and DL designed the current study, conducted the analyses and drafted the manuscript; CB, GM contributed to the statistical analysis and interpretation of the results. DC, CP, 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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Title: Head and neck cancer and occupational exposure to solvents in women: results from the ICARE study

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: 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 five 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). Odds ratio (ORs) and 95% confidence intervals (CI), adjusted for smoking, alcohol drinking, age and department, were estimated with logistic models.

Results: Elevated ORs were observed among women ever exposed to perchloroethylene (OR=2.97, 95%CI: 1.05-8.45) and trichloroethylene (OR=2.15, 95%CI: 1.21-3.81). These ORs increased with exposure duration- (respectively OR=3.75, 95%CI: 0.64-21.9 and OR=4.44, 95%CI: 1.56-12.6 for ten years or more). 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.

Keywords: head and neck; cancer; trichloroethylene; perchloroethylene; occupational exposures; women; solvents

Strengths and limitations

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 nondifferential.

Despite a relatively large number of cases, statistical power was limited for in-depth analyses by cancer sites.

Data sharing statement: No additional data are available.

Introduction

Compared to other European Union countries, head and neck cancers are frequent in France [1]. Age-standardized (world population) incidence rates in 2012 in France were 16.1 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 [25], perchloroethylene [25] or benzene [26] are classified as proven or probable carcinogens by 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]. ICARE (Investigation of occupational and environmental CAuses of REspiratory cancers), 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 multi-center, 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 lip, oral cavity and pharynx (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 both head and neck cancer and lung cancer cases, and a distribution by socioeconomic status comparable to that of the general population. Subjects were interviewed face to face, using a standardized 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. 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 by the French Data Protection Authority (CNIL n° 90120).

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: i) oral cavity, 88 cases (29.7%): ICD-O-3 codes C00.3 – C00.9, C02.0 – C02.3, C03, C04, C05.0 and C06; ii) oropharynx, 111 cases (37.5%): codes C01.9, C02.4, C05.1, C05.2, C09 and C10; iii) hypopharynx, 28 cases (9.5%): codes C12-C13; iv) oral cavity, pharynx unspecified or overlapping, 22 cases (7.4%): codes C02.8, C02.9, C05.8, C05.9 and C14; v) 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 one 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; perchloroethylene; trichloroethylene), 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: (*i*) probability of exposure expressed as the percentage of exposed workers (*ii*) intensity of exposure and (*iii*) frequency of exposure. For these three indices, different categories were used depending on the solvent considered (See Supplementary material: Table S-I).

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 greater than zero. 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 categorized (cutpoints: 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.

Because of the low exposure prevalence for most solvents among women, we favored 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 odds ratios (ORs) and corresponding 95% confidence intervals (95% CI) of head and neck cancers. Analyses were adjusted for geographic 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 socioeconomic status (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 odds ratios 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 I. On average, cases were 2 years younger than controls. This is explained by the fact that controls were stratified on age (in four categories: less than 40 years, 40-54 years, 55-64 years and >65 years) based on the age distribution of both head and neck cancer cases and lung cancer cases. The socioeconomic status of cases was lower than that of controls. Cases were less likely to be never smokers or never drinkers than controls. Table II 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 respectively 32% and 48% of the controls were exposed.

Ever exposure to trichloroethylene and to perchloroethylene was associated with significantly elevated ORs. No other significant association was found. Additional analyses using a more specific cutpoint to define ever exposure (probability > 10% for methylene chloride, probability>30% for trichloroethylene, probability > 50% for the other solvents) produced similar results, although the confidence intervals 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 III.

Chlorinated solvents

The risk of head and neck cancer increased with the duration of exposure to trichloroethylene (Table III). A similar increase in risk with duration of exposure was found for exposure to perchloroethylene. No clear relationship was observed between head and neck cancer and average intensity or cumulative exposure to trichloroethylene 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 perchloroethylene, average intensity and cumulative exposure were not associated with head and neck cancer.

The distribution of job periods exposed to trichloroethylene by occupation (See 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 trichloroethylene 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 trichloroethylene and benzene. The OR for trichloroethylene 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 perchloroethylene by occupation (See Supplementary material: Figure 2) shows that the most frequently exposed occupations were dry cleaners launderers, degreasers, assemblers in electrical and electronic equipment. The most frequent sector of activity was laundry and dry cleaning.

Exposures to trichloroethylene and perchloroethylene were strongly correlated, and were also correlated to methylene chloride exposure, which makes the interpretation of mutually adjusted ORs difficult. Instead, we studied exposure to exclusive combinations of chlorinated solvents (Table IV). No case was exposed only to perchloroethylene. The odds ratio associated with trichloroethylene alone was high (OR=1.81, 95% CI 0.81 to 4.04), but lower than in the analysis reported in Table II (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 trichloroethylene and perchloroethylene (OR=4.47, 95% CI 1.27 to 15.8).

Analyses by cancer sites are presented in Table V. The OR associated with trichloroethylene 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 dose-response relation with duration and cumulative exposure (See Supplementary material: Table S-II, 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. Perchloroethylene 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 II) 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 III). Exposure to white-spirit (Table V) 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 Supplementary material: Table S-III)

Oxygenated solvents

With regards to oxygenated solvents (Table II), 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 III). 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 Supplementary material: Table S-IV).

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 trichloroethylene and perchloroethylene, with high and significant risks. For trichloroethylene 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 perchloroethylene 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.

Trichloroethylene (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, etc. 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 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-Nielsen [35] found SIRs of 1.8 for buccal cavity and pharynx cancers (10 observed) and 1.7 for larynx cancers (3 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 SMR for buccal cavity and pharynx cancers (4 observed) and for larynx cancers (2 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 a 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 (8 observed) and among women (2 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 vs not exposed to TCE among men (11 exposed cases, OR=1.23, 95% CI 0.34 to 4.43) and among women (2 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, perchloroethylene (PCE), another widely used chlorinated solvent, was used extensively in dry cleaning but also for 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 (4 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 joint exposure to both TCE and PCE (9 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 etiology. 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 our knowledge, these associations have not be 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 characterized 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. Because 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 HPV 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, do 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 odds ratio biased towards 1, with an associated loss of statistical power for dichotomized 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 JEMs [33] 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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Table I: Main characteristics of cases and controls

	Cases		Controls	
	n	%	n	%
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 (56.9-59.0)		60.4 (59.6-61.2)	
Class				
<50 years	51	17.2	160	20.6
50-59.9 years	109	36.8	157	20.3
60-69.9 years	99	33.4	246	31.8
≥ 70 years	37	12.6	212	27.3
Number of jobs held				p=0.01
Mean (95%CI)	3.3 (2.9-3.6)		3.7 (3.4-3.8)	
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	-

*: Nonsmokers 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).

Table II: Association between head and neck cancer and ever exposure to solvents

	Never exposed				Ever exposed				OR#	
	Cases		Controls		Cases		Controls			
	n	%	n	%	n	%	n	%		
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
Tetrahydrofurane	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, department, alcohol and tobacco consumption.

Table III: 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				Continuous		< 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	OR#	95% CI
Chlorinated solvents																																
Methylene chloride	1	Ref.	7	21	0.85	0.28-2.56	7	9	1.65	0.42-6.53	0.99	0.93-1.05	4	19	0.62	0.18-2.16	10	11	2.02	0.60-6.84	1.23	0.77-1.97	7	15	1.34	0.42-4.28	7	15	0.87	0.25-2.99	1.01	0.97-1.06
Trichloroethylene	1	Ref.	25	47	1.67	0.86-3.24	13	13	4.44	1.56-12.6	1.06	1.01-1.12	24	30	2.62	1.24-5.54	14	30	1.67	0.71-3.90	1.30	1.01-1.66	20	30	2.16	1.02-4.58	18	30	2.13	0.94-4.84	1.02	1.01-1.04
Perchloroethylene	1	Ref.	8	9	2.66	0.75-9.40	2	4	3.75	0.64-21.9	1.06	0.97-1.17	4	7	3.56	0.90-14.1	6	6	2.38	0.51-11.2	1.08	0.95-1.23	8	7	4.09	1.15-14.6	2	6	1.44	0.18-11.6	1.00	0.99-1.02
Petroleum solvents																																
Special petroleum product	1	Ref.	19	30	1.47	0.67-3.20	8	24	1.30	0.47-3.65	0.99	0.94-1.04	18	27	1.30	0.56-3.01	9	27	1.54	0.61-3.89	1.01	0.93-1.11	21	27	1.51	0.68-3.35	6	27	1.25	0.45-3.45	1.00	0.99-1.01
Diesel	1	Ref.	12	16	2.89	1.03-8.08	2	10	0.56	0.09-3.31	1.02	0.95-1.10	8	14	1.56	0.49-4.97	6	12	2.13	0.59-7.61	1.30	0.94-1.78	6	12	1.14	0.31-4.29	8	14	2.52	0.82-7.74	1.00	0.97-1.03
Benzene	1	Ref.	21	35	1.77	0.85-3.67	7	15	1.34	0.38-4.68	1.00	0.94-1.06	20	28	1.52	0.67-3.43	8	22	1.87	0.71-4.96	1.38	0.36-5.22	19	25	1.59	0.69-3.64	9	25	1.74	0.67-4.53	1.02	0.89-1.17
White-spirits	1	Ref.	50	153	0.87	0.54-1.40	37	94	1.45	0.83-2.52	1.01	0.99-1.04	62	182	1.08	0.70-1.67	25	64	0.96	0.49-1.86	0.94	0.74-1.20	42	118	1.04	0.62-1.74	45	129	1.08	0.65-1.78	1.00	0.98-1.02
Oxygenated solvents																																
Diethyl ether	1	Ref.	9	25	1.07	0.39-2.91	16	63	0.52	0.25-1.07	0.98	0.95-1.01	12	44	0.58	0.25-1.33	13	44	0.73	0.32-1.67	0.01	0.00-326	13	44	0.89	0.41-1.95	12	44	0.46	0.19-1.10	0.70	0.41-1.27
Ketones	1	Ref.	32	55	1.71	0.94-3.11	12	28	1.42	0.58-3.48	1.02	0.98-1.06	22	42	1.68	0.81-3.46	22	41	1.56	0.79-3.06	1.11	0.92-1.35	28	42	2.27	1.16-4.44	16	41	1.10	0.52-2.31	1.01	0.99-1.02
Alcohols	1	Ref.	67	168	0.93	0.59-1.45	56	196	0.71	0.44-1.13	0.99	0.97-1.01	80	255	0.76	0.50-1.15	43	109	0.89	0.53-1.51	1.33	0.90-1.95	57	180	0.68	0.43-1.10	66	184	0.95	0.61-1.48	1.01	0.98-1.03

Ref.: Women who have never been exposed to the current solvent are the reference category.

OR adjusted for age at interview, department, alcohol and tobacco consumption.

Table IV: 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

TRI: trichloroethylene, PER: perchloroethylene, MC: methylene chloride

OR adjusted for age at interview, department, alcohol and tobacco consumption.

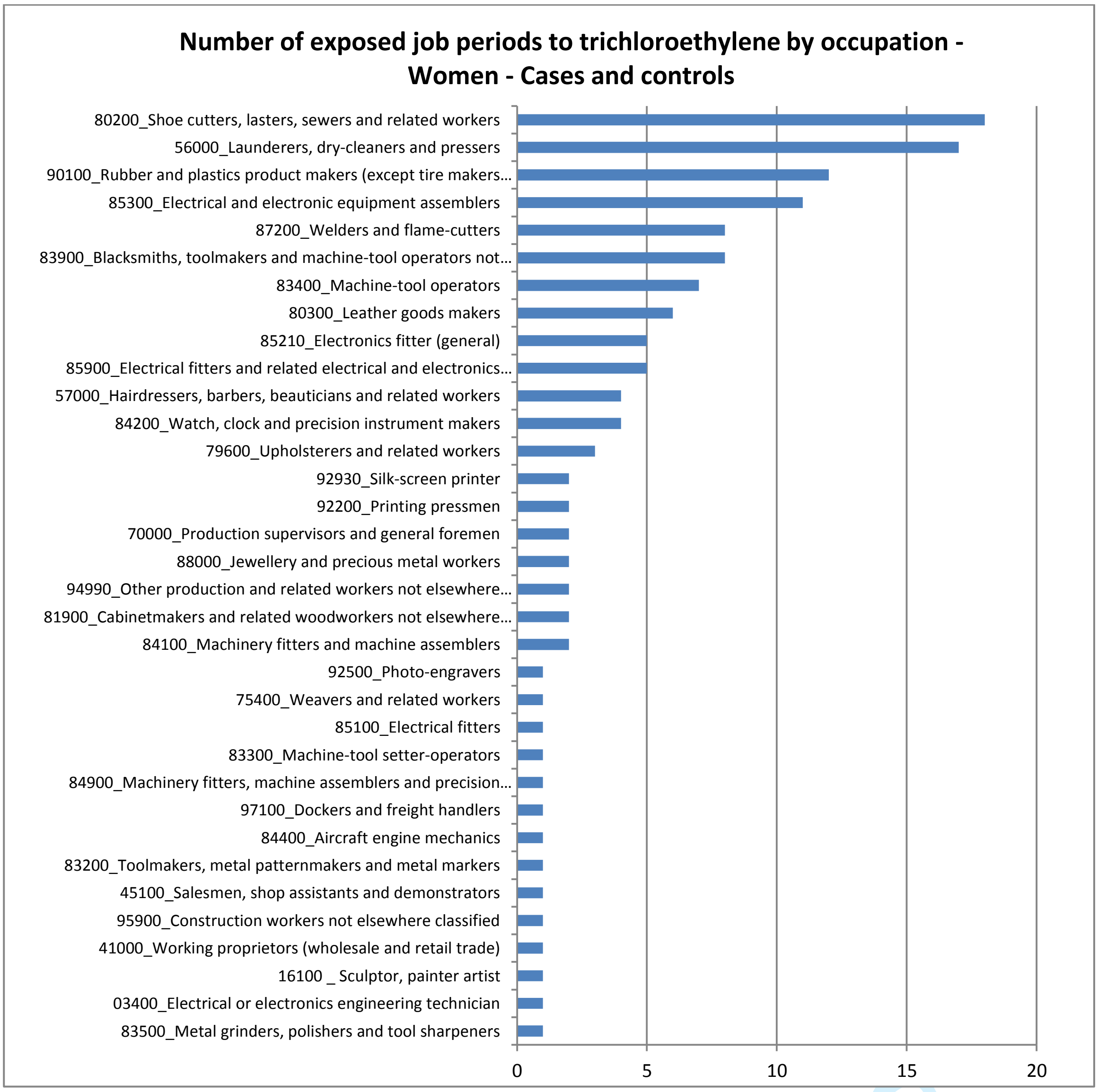
Table V: Association between head and neck cancer sites and ever exposure to selected solvents

		Oral cavity			Oropharynx			Hypopharynx			Larynx		
Ever exposure to	Controls	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

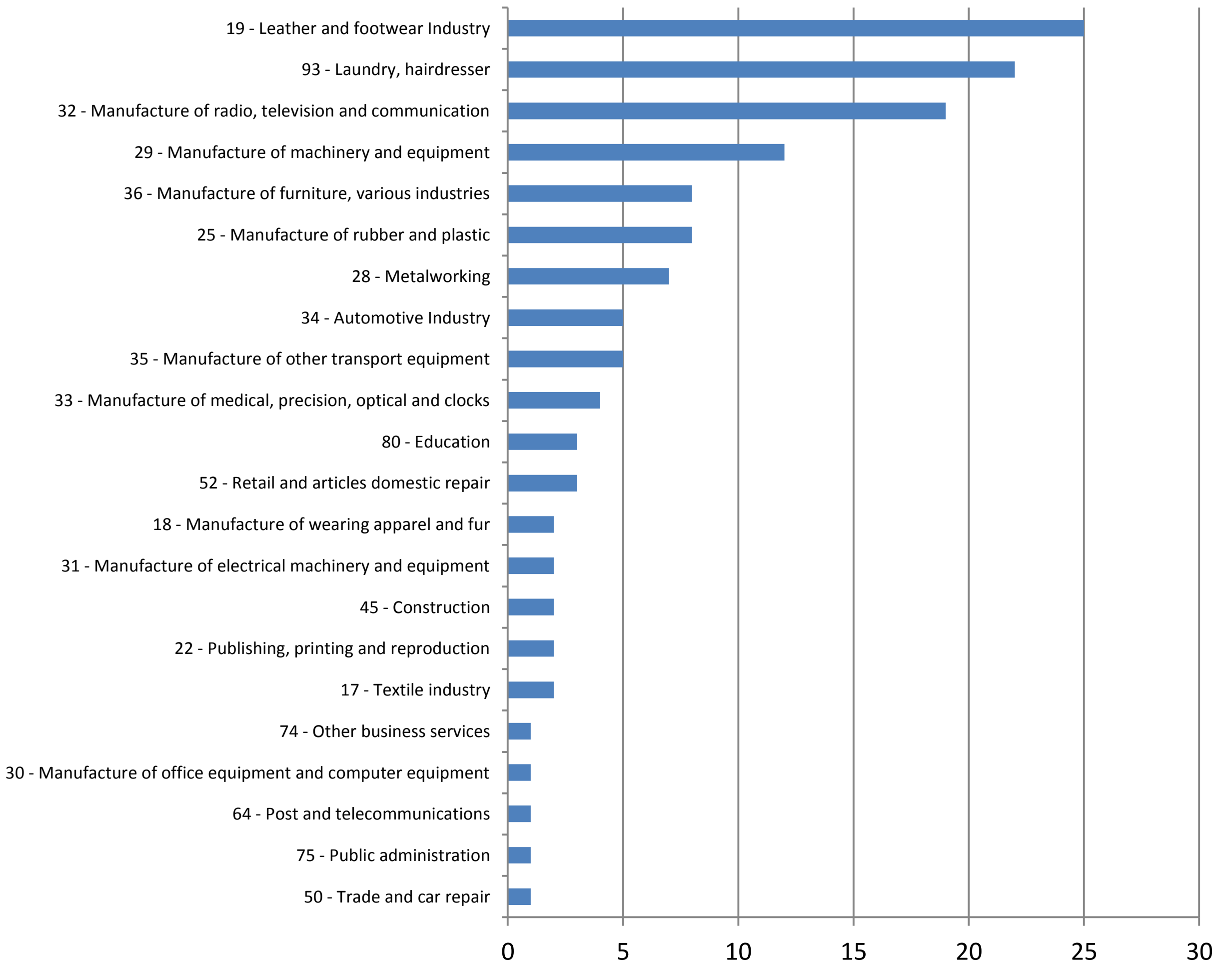
OR adjusted for age at interview, department, alcohol and tobacco consumption.

SUPPLEMENTARY MATERIALS

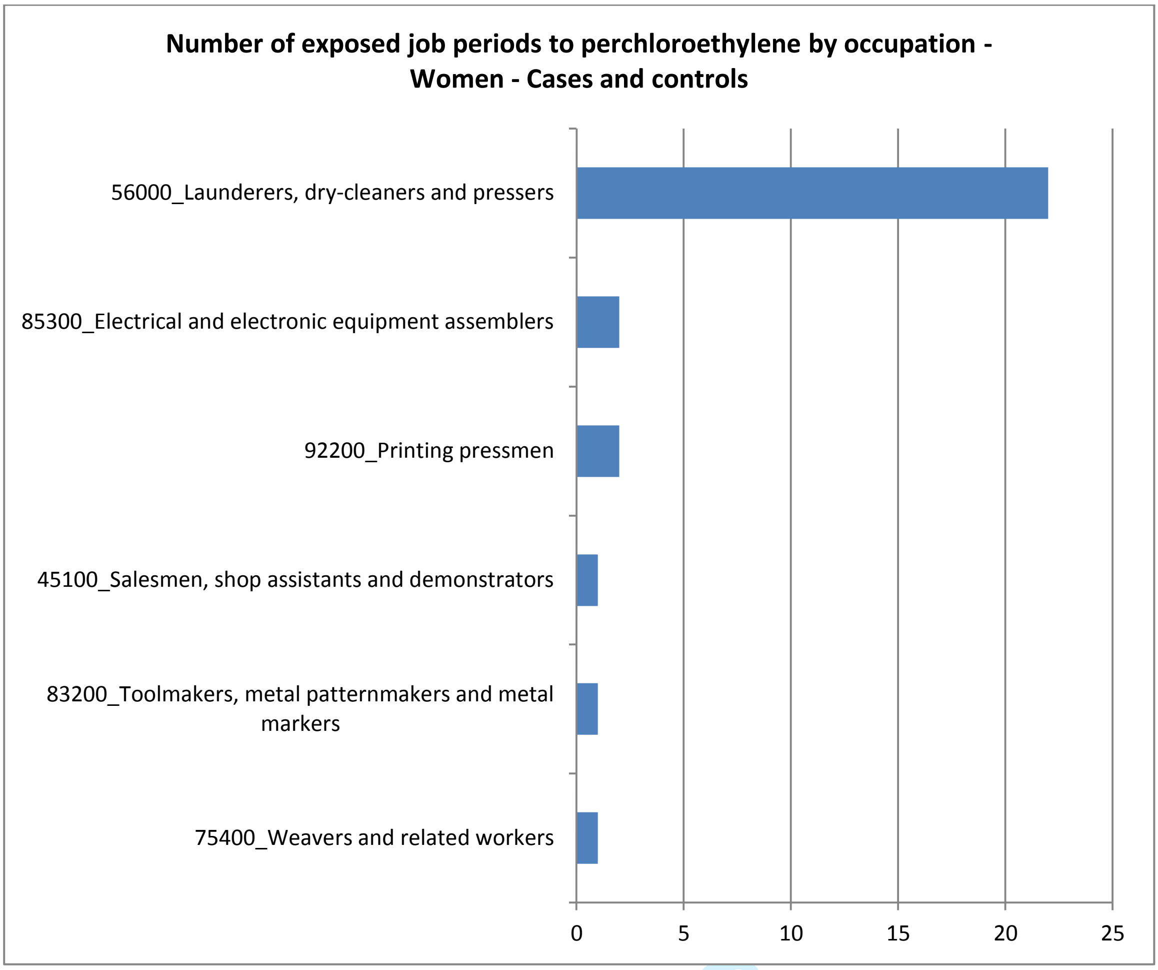
Supplementary - Figures 1



Number of exposed job periods to trichloroethylene by industry - Women - Cases and controls



Supplementary - Figures 2



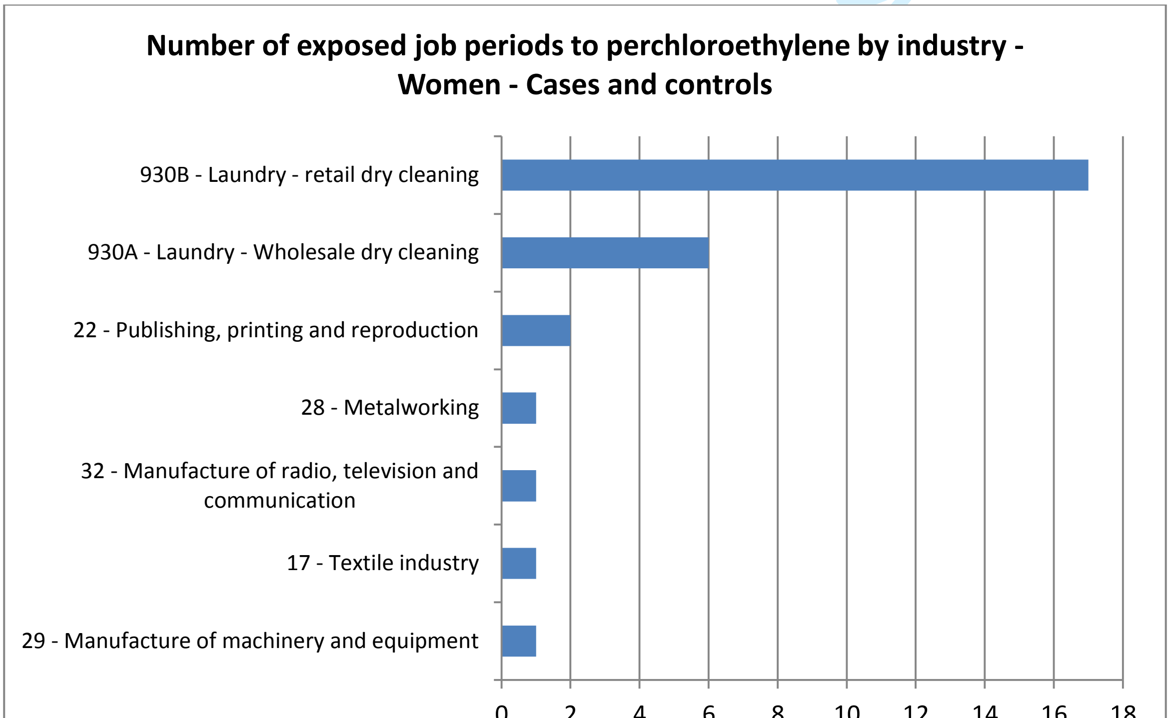


Table S-I: Categories of exposure indices for solvents

	Probability of exposure	Intensity of exposure	Frequency of exposure
Chloroform	<1%; 1–10%; 11–20%; 21–30%;…; up to 91–100%	not exposed; very low; low; medium; high	<1%; 1–10%; 11–20%; 21–30%;…; up to 91–100%
Carbon tetrachloride			
Methylene chloride		<5; 5–25; 26–50; 51–100; >100 ppm	
Trichloroethylene			
Perchloroethylene			
Motors gasoline	<1%; 1–10%; 11–50%; 50–90%; >90%	not exposed; low; medium; high	<0.5%; 0.5–5%; 5–30%; 30–70%; >70%
Special petroleum product			
Diesel			
Benzene		<0.1 ; 0.1–1 ; 1–5 ; 5–15 ; >15 ppm	
White-spirits		<1 ; 1–20 ; 20–50 ; >50 ppm	
Ethylene glycol	<1%; 1–10%; 11–20%; 21–30%;…; up to 91–100%	not exposed; low; medium; high	<1%; 1–10%; 11–20%; 21–30%;…; up to 91–100%
Tetrahydrofurane			
Diethyl ether		not exposed; very low; low; medium; high	
Ketones			
Alcohols			

Table S-II: Association between head and neck cancer site and exposure to chlorinated solvents

		Oral cavity				Oropharynx				Hypopharynx				Larynx			
	Controls	Cases	OR#	CI 95%	p	Cases	OR#	CI 95%	p	Cases	OR#	CI 95%	p	Cases	OR#	CI 95%	p
Methylene chloride																	
Ever exposed	30	5	1.34	0.44 to 4.13	0.60	2	0.42	0.09 to 2.02	0.28	2	1.23	0.21 to 7.18	0.81	4	2.0	0.56 to 7.20	0.28
Cumulative Exposure Index																	
< median	15	2	1.39	0.27 to 7.16	0.69	2	0.92	0.17 to 4.94	0.92	-	-	-	-	3	3.12	0.65 to 14.9	0.15
≥ median	15	3	1.30	0.29 to 5.90	0.73	-	-	-	-	2	1.78	0.24 to 13.5	0.57	1	0.95	0.10 to 9.29	0.96
Duration of exposure																	
< 10 years	21	2	0.79	0.16 to 4.05	0.78	1	0.32	0.04 to 2.75	0.30	1	1.11	0.10 to 12.0	0.93	3	2.35	0.54 to 10.3	0.25
≥ 10 years	9	3	2.52	0.52 to 12.3	0.25	1	0.64	0.06 to 6.36	0.70	1	1.53	0.12 to 19.6	0.74	1	1.52	0.14 to 16.7	0.73
Trichloroethylene																	
Ever exposed	60	12	2.12	0.97 to 4.60	0.058	13	1.66	0.78 to 3.54	0.18	3	2.45	0.57 to 10.5	0.22	**10**	**3.80**	**1.55 to 9.32**	**0.003**
Cumulative Exposure Index																	
< median	30	4	1.38	0.42 to 4.57	0.59	9	2.30	0.93 to 5.71	0.07	1	1.22	0.12 to 12.1	0.86	**6**	**4.22**	**1.34 to 13.3**	**0.013**
≥ median	30	**8**	**2.73**	**1.02 to 7.30**	0.04	4	0.97	0.27 to 3.42	0.96	2	4.13	0.72 to 23.7	0.11	4	3.25	0.92 to 11.4	0.067
Duration of exposure																	
< 10 years	47	6	1.16	0.42 to 3.22	0.78	9	1.48	0.62 to 3.49	0.37	3	2.31	0.52 to 10.3	0.27	**8**	**3.47**	**1.28 to 9.41**	**0.014**
≥ 10 years	13	**6**	**6.84**	**2.11 to 22.1**	0.001	4	2.54	0.63 to 10.3	0.19	0	-	-	-	2	4.73	0.86 to 26.0	0.074
Perchloroethylene																	
Ever exposed	13	1	0.98	0.11 to 8.47	0.98	**5**	**3.43**	**1.01 to 11.8**	**0.05**	0	-	-	-	**4**	**7.95**	**1.92 to 32.9**	**0.004**
Cumulative Exposure Index																	
< median	7	1	1.59	0.17 to 14.7	0.68	3	3.76	0.75 to 18.9	0.11	0	-	-	-	**4**	**15.8**	**3.19 to 77.8**	**0.0007**
≥ median	6	0	-	-	0.99	2	2.59	0.32 to 20.7	0.36	0	-	-	-	0	-		-
Duration of exposure																	
< 10 years	9	0	-	-	0.99	4	3.55	0.80 to 15.7	0.09	0	-	-	-	**4**	**9.96**	**2.04 to 48.5**	**0.004**
≥ 10 years	4	1	9.50	0.89 to 101	0.06	1	3.22	0.33 to 31.5	0.31	0	-	-	-	0	-		-

OR adjusted for age at interview, department, alcohol and tobacco consumption.

Table S-III: Association between head and neck cancer site and exposure to petroleum solvents

	Controls	Oral cavity				Oropharynx				Hypopharynx				Larynx			
		Cases	OR#	CI 95%	p	Cases	OR#	CI 95%	p	Cases	OR#	CI 95%	p	Cases	OR#	CI 95%	p
Special petroleum product																	
Ever exposed	54	10	1.79	0.78 to 4.09	0.17	7	0.87	0.35 to 2.17	0.76	2	1.05	0.19 to 5.78	0.95	**7**	2.24	0.82 to 6.09	0.11
Cumulative Exposure Index																	
< median	27	7	1.86	0.66 to 5.25	0.24	5	0.86	0.28 to 2.63	0.79	2	1.43	0.24 to 8.63	0.69	**7**	**3.12**	**1.04 to 9.33**	**0.042**
≥ median	27	3	1.81	0.50 to 6.59	0.37	2	0.96	0.20 to 4.57	0.95	0	-	-	-	0	-	-	-
Duration of exposure																	
< 10 years	30	5	1.30	0.43 to 3.97	0.64	6	1.12	0.39 to 3.18	0.83	1	0.79	0.08 to 7.41	0.83	**7**	**3.31**	**1.12 to 9.74**	**0.030**
≥ 10 years	24	5	2.75	0.85 to 8.85	0.091	1	0.39	0.05 to 3.19	0.38	1	1.55	0.13 to 19.0	0.73	0	-	-	-
Gasoil																	
Ever exposed	26	2	0.88	0.18 to 4.32	0.87	5	1.90	0.60 to 6.03	0.27	2	3.60	0.55 to 23.4	0.18	4	2.51	0.66 to 9.53	0.17
Cumulative Exposure Index																	
< median	12	0	-	-	0.99	3	1.81	0.38 to 8.53	0.45	1	3.24	0.24 to 44.3	0.37	2	1.62	0.25 to 10.6	0.61
≥ median	14	2	1.91	0.37 to 9.78	0.44	2	1.80	0.33 to 9.88	0.49	1	3.57	0.27 to 47.1	0.33	2	3.60	0.62 to 20.7	0.15
Duration of exposure																	
< 10 years	16	2	1.62	0.30 to 8.65	0.57	4	3.02	0.80 to 11.5	0.10	1	3.38	0.28 to 41.1	0.33	**4**	**4.42**	**1.04 to 18.8**	**0.045**
≥ 10 years	10	0	-	-	0.99	1	0.62	0.06 to 6.36	0.68	1	4.87	0.33 to 71.7	0.24	0	-	-	-
Benzene																	
Ever exposed	50	9	1.79	0.76 to 4.22	0.18	9	1.39	0.58 to 3.31	0.45	2	0.97	0.17 to 5.43	0.97	6	2.07	0.72 to 5.97	0.17
Cumulative Exposure Index																	
< median	25	6	1.86	0.63 to 5.52	0.26	6	1.17	0.40 to 3.43	0.77	1	0.78	0.08 to 7.72	0.82	5	2.57	0.75 to 8.79	0.13
≥ median	25	3	1.62	0.42 to 6.22	0.48	3	2.06	0.53 to 8.01	0.29	1	1.21	0.10 to 14.8	0.88	1	0.90	0.09 to 8.79	0.92
Duration of exposure																	
< 10 years	35	5	1.47	0.51 to 4.29	0.48	8	1.72	0.67 to 4.42	0.25	1	0.87	0.09 to 8.12	0.90	6	**3.03**	**1.02 to 9.18**	**0.050**
≥ 10 years	15	4	2.32	0.57 to 9.48	0.24	1	0.56	0.06 to 5.07	0.60	1	0.93	0.06 to 13.6	0.95	0	-	-	-
White-spirits																	
Ever exposed	247	32	1.54	0.90 to 2.66	0.12	**21**	**0.54**	**0.30 to 0.95**	**0.03**	10	1.67	0.65 to 4.29	0.28	20	1.76	0.86 to 3.37	0.12
Cumulative Exposure Index																	
< median	117	12	1.20	0.56 to 2.54	0.64	10	0.53	0.25 to 1.15	0.10	8	2.75	0.91 to 8.32	0.074	10	1.76	0.75 to 4.17	0.19
≥ median	129	20	1.75	0.91 to 3.37	0.09	11	0.51	0.23 to 1.09	0.08	2	0.52	0.10 to 2.71	0.43	10	1.70	0.71 to 4.06	0.23
Duration of exposure																	
< 10 years	152	14	0.97	0.48 to 1.96	0.93	**11**	**0.41**	**0.20 to 0.85**	**0.02**	9	2.02	0.70 to 5.84	0.19	14	1.68	0.77 to 3.64	0.19
≥ 10 years	94	**18**	**2.51**	**1.25 to 5.02**	**0.009**	10	0.75	0.33 to 1.69	0.48	1	0.47	0.05 to 4.23	0.50	6	1.73	0.62 to 4.83	0.29

OR adjusted for age at interview, department, alcohol and tobacco consumption.

Table S-IV: Association between head and neck cancer site and exposure to oxygenated solvents

		Oral cavity				Oropharynx				Hypopharynx				Larynx			
	Controls	Cases	OR#	CI 95%	p	Cases	OR#	CI 95%	p	Cases	OR#	CI 95%	p	Cases	OR#	CI 95%	p
Diethyl ether																	
Ever exposed	88	10	0.91	0.41 to 2.06	0.83	8	0.51	0.22 to 1.20	0.12	3	0.74	0.18 to 3.05	0.67	2	0.30	0.07 to 1.40	0.12
Cumulative Exposure Index																	
< median	44	6	1.57	0.56 to 4.42	0.39	3	0.47	0.13 to 1.69	0.24	1	0.64	0.07 to 5.82	0.69	1	0.43	0.05 to 3.46	0.42
≥ median	44	4	0.51	0.15 to 1.74	0.28	5	0.51	0.17 to 1.56	0.24	2	0.73	0.12 to 4.58	0.74	1	0.21	0.03 to 1.86	0.16
Duration of exposure																	
< 10 years	25	4	1.49	0.42 to 5.35	0.54	2	0.64	0.13 to 3.09	0.57	1	0.98	0.10 to 9.76	0.98	1	0.77	0.09 to 6.62	0.81
≥ 10 years	63	6	0.71	0.26 to 1.95	0.50	6	0.46	0.18 to 1.24	0.12	2	0.65	0.12 to 3.64	0.62	1	0.18	0.02 to 1.48	0.11
Ketones																	
Ever exposed	83	13	1.58	0.77 to 3.25	0.22	14	1.24	0.62 to 2.48	0.54	5	1.93	0.59 to 6.26	0.27	**11**	**2.66**	**1.17 to 6.07**	**0.020**
Cumulative Exposure Index																	
< median	42	8	2.08	0.83 to 5.23	0.13	10	1.94	0.82 to 4.58	0.12	**4**	**4.37**	**1.13 to 16.9**	**0.032**	**7**	**3.46**	**1.24 to 9.65**	**0.018**
≥ median	41	5	1.17	0.40 to 3.42	0.77	4	0.65	0.21 to 2.07	0.47	1	0.51	0.05 to 4.87	0.55	4	2.04	0.60 to 6.98	0.25
Duration of exposure																	
< 10 years	55	8	1.35	0.56 to 3.26	0.50	11	1.43	0.65 to 3.15	0.38	3	1.70	0.42 to 6.95	0.45	**10**	**3.34**	**1.38 to 8.10**	**0.008**
≥ 10 years	28	5	2.19	0.70 to 6.81	0.18	3	0.85	0.23 to 3.20	0.81	2	2.46	0.37 to 16.4	0.35	1	0.93	0.11 to 7.99	0.95
Alcohols																	
Ever exposed	365	41	1.02	0.61 to 1.73	0.93	**40**	**0.59**	**0.36 to 0.97**	**0.03**	15	1.43	0.57 to 3.56	0.44	22	0.89	0.46 to 1.75	0.74
Cumulative Exposure Index																	
< median	180	17	0.80	0.41 to 1.58	0.52	**18**	**0.4**	**0.25 to 0.91**	**0.02**	11	1.86	0.67 to 5.16	0.23	11	0.77	0.34 to 1.77	0.54
≥ median	184	24	1.22	0.66 to 2.27	0.53	22	0.68	0.37 to 1.25	0.21	4	0.73	0.20 to 2.70	0.63	11	1.03	0.45 to 2.37	0.93
Duration of exposure																	
< 10 years	168	20	1.05	0.55 to 2.01	0.87	20	0.62	0.34 to 1.15	0.12	10	1.91	0.68 to 5.38	0.22	15	1.24	0.58 to 2.64	0.58
≥ 10 years	196	21	0.96	0.51 to 1.83	0.90	20	0.54	0.29 to 1.01	0.055	5	0.82	0.23 to 2.87	0.75	7	0.57	0.22 to 1.46	0.24

OR adjusted for age at interview, department, alcohol and tobacco consumption.

STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation	Page in main doc
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	7-8
		(*b*) For matched studies, give matching criteria and the number of controls per case	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*9*
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10-11
		(*b*) Describe any methods used to examine subgroups and interactions	10-11
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how matching of cases and controls was addressed	
		(*e*) Describe any sensitivity analyses	11
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	X
		(b) Give reasons for non-participation at each stage	X
		(c) Consider use of a flow diagram	X
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12 + Table I
		(b) Indicate number of participants with missing data for each variable of interest	12 + Table I
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	Table II
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates	12-14 +

	and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Tables
	(*b*) Report category boundaries when continuous variables were categorized	Tables
	(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14 + Tables and Suppl. Mat
Discussion			
Key results	18	Summarise key results with reference to study objectives	16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	20-21
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	22
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.