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Occupation and risk of upper aerodigestive tract cancer: The ARCAGE study

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Abstract

We investigated the association between occupational history and upper aerodigestive tract (UADT) cancer risk in the ARCAGE European case–control study. The study included 1,851 patients with incident cancer of the oral cavity, oropharynx, hypopharynx, larynx or esophagus and 1,949 controls. We estimated odds ratios (OR) and 95% confidence intervals (CI) for ever employment in 283 occupations and 172 industries, adjusting for smoking and alcohol. Men (1,457 cases) and women (394 cases) were analyzed separately and we incorporated a semi-Bayes adjustment approach for multiple comparisons. Among men, we found increased risks for occupational categories previously reported to be associated with at least one type of UADT cancer, including painters (OR = 1.74, 95% CI: 1.01–3.00), bricklayers (1.58, 1.05–2.37), workers employed in the erection of roofs and frames (2.62, 1.08–6.36), reinforced concreters (3.46, 1.11–10.8), dockers

(2.91, 1.05–8.05) and workers employed in the construction of roads (3.03, 1.23–7.46), general construction of buildings (1.44, 1.12–1.85) and cargo handling (2.60, 1.17–5.75). With the exception of the first three categories, risks both increased when restricting to long duration of employment and remained elevated after semi-Bayes adjustment. Increased risks were also found for loggers (3.56, 1.20–10.5) and cattle and dairy farming (3.60, 1.15–11.2). Among women, there was no clear evidence of increased risks of UADT cancer in association with occupations or industrial activities. This study provides evidence of an association between some occupational categories and UADT cancer risk among men. The most consistent findings, also supported by previous studies, were obtained for specific workers employed in the construction industry.
Alcohol drinking and tobacco smoking are the two main risk factors for cancers of the upper aerodigestive tract (UADT), which group together tumors originating in the oral cavity, pharynx, larynx and esophagus.1–3 These two exposures may explain up to 75% of all UADT cancer cases.3 Diet,4 human papillomavirus (HPV) infection,5 low socioeconomic status6 and genetic susceptibility7 have all been indicated as other potential risk factors.
A number of case–control studies have investigated occupational exposures in relation to the risk of UADT cancer.8–23 Most of these studies had a limited sample size and focused on laryngeal cancer only. Increased risks have been repeatedly found for a number of occupations, including painters,9–12, 24 specific categories of construction workers,9–14, 16, 17 metal workers,9–14 laborers,9, 11, 13–16, 18, 19 butchers14, 21 and shoe, leather and textile workers14, 15, 19, 21, 23–25 as well as for exposure to some specific occupational agents, such as sulfuric acid, asbestos and coal dust.20, 26, 27
We used data from a large multicenter case–control study recently conducted in 14 centers throughout Europe, in which a detailed occupational history was collected using a standardized questionnaire, to further investigate the role for occupational factors in UADT cancer etiology.

Methods

Study design and exposure information

ARCAGE (Alcohol Related Cancers and Genetic Susceptibility in Europe) is a European multicenter case–control study on UADT cancer carried out between 2000 and 2005 in 14 centers in 10 European countries, including Czech Republic, Croatia, France (in which recruitment was conducted between 1987 and 1992), Germany, Greece, Ireland, Italy, Norway, Spain and the UK. It was approved by the ethical committee of the coordinating centre (International Agency for Research on Cancer, Lyon, France) and the local ethical committees at each participating center. A detailed description of the study methods has been published before.28
The study was hospital-based in most of the countries, with the exception of the three UK centers in which a population-based approach was used. In each centre, cases included all newly diagnosed primary cancers occurring in the oral cavity (ICD-O-3: C00–C06), oropharynx (C09, C10), hypo-pharynx (C12, C13), larynx (C14, C32) or esophagus (C15) identified by constant monitoring at the hospitals and clinics participating in the study. All cases were histologically confirmed.
Controls were frequency-matched to cases by 5-year age groups, sex and center. Hospital controls were selected among patients admitted for diseases unrelated to tobacco or alcohol. Eligible diagnoses included endocrine and metabolic disorders as well as genito-urinary, skin, subcutaneous tissue and musculoskeletal diseases, gastro-intestinal, circulatory, ear, eye and mastoid diseases, nervous system diseases, trauma and plastic surgery patients. The proportion of controls within a specific diagnostic group should not exceed 33% of the total in any center. In the UK, population controls were randomly selected from a list of individuals registered with the same general practitioner as the corresponding cases. In the Paris center, the source population was limited to smokers.
We used a face-to-face interview and a standardized questionnaire to obtain information from all study subjects on demographic characteristics, educational level, lifetime smoking, alcohol

consumption, diet, medical history, anthropometric measures and full occupational history. For each occupational period that lasted at least 6 months, we recorded the year of beginning and end as well as the descriptions of the job title and the branch of industry. Part-time and seasonal jobs were recorded.
In each country, a trained coder codified the occupational periods blinded to case–control status according to the National Industrial Classification of All Economic Activities (NACE)29 for branches of industry and the International Standard Classification of Occupations (ISCO)30 for the job titles. These classifications, based on four and five digits respectively, increase the specificity of each occupation/industry with increasing number of digits. The Paris center had coded occupational histories differently, namely using 3-digit ISCO codes for the job titles and the ISIC-2 classification for the branches of industries. We therefore excluded the Paris center from the main analyses, although we carried out a separated analysis based on 3-digit ISCO codes among the 297 male cases and the 210 male controls from Paris to check for consistency with the results obtained on all other centers.

Statistical analyses

Overall, 1,981 cases and 1,993 controls participated in the study with a response proportion of 82% among cases and 68% among controls. We excluded 77 cases with adenocarcinoma of the esophagus and 18 subjects with *in-situ* carcinoma. Moreover, we excluded all case and control subjects with missing values in smoking, alcohol consumption and/or educational level (27 cases and 32 controls). Another 8 cases and 12 controls were excluded because they had no information on their occupational history, thus leaving 1,851 cases and 1,949 controls for the present analyses. We carried out analyses in men (1,457 cases and 1,425 controls) and women (394 cases and 524 controls) separately and used multivariable logistic regression to estimate odds ratios of UADT cancer, with corresponding 95% confidence intervals (95% CI), for ever compared with never employment in each occupational or industrial category. We considered a lag time of 10 years, thus exposures occurring in the last ten years before the interview were not considered, and analyzed only categories including at least 10 exposed subjects. All models included centre, age, cigarette smoking and alcohol consumption. These variables were categorized as reported in Table 1. As previously suggested,31 we estimated each odds ratio (OR) in models with and without adjustment for attained educational level. All UADT cancer cases were grouped together in the main analyses while we conducted secondary analyses considering the three main subsites separately (mouth and oropharynx, hypopharynx and larynx, esophagus). Analyses were conducted using the software SAS®, version 9.

Since we considered a large number of occupations and industries, we also applied a semi-Bayes (SB) approach,32, 33 using *R* software, to identify the most robust estimates. We assumed a variance of the true Log ORs of 0.25 and shrunk the estimates for each category towards the overall mean, for the industries, and towards a group mean, for the occupations, where we used two groups, namely blue-collar worker and white-collar worker occupations.

Results

Characteristics of cases and controls are reported in Table 1. Tobacco smoking and alcohol consumption were higher among cases than controls both in men and women. Cases had a lower educational level, while the mean number of job periods was similar between cases and controls. Among men and women combined, 49% of the UADT cancers occurred in the oral cavity/oropharynx, 37% in the hypopharynx/larynx, 9% in the esophagus and 5% were classified as overlapping cancers.

Men

Overall, we evaluated 283 occupational categories (3 and 5 digits, Supporting Information Table S1), 17 of which were associated with UADT cancer risk with a *p*-value below 0.05 in smoking- and alcohol-adjusted analyses. Out of these, 10 categories were associated with an increased risk (Table 2). For a number of these occupations, namely loggers, electronic fitters, reinforced concreters, dockers, lorry and van drivers and labourers, risk estimates further increased when we restricted analyses to subjects employed for at least 10 years. With the exception of concreters and bricklayers, adjustment for educational level had limited impact on OR estimates. When we applied shrinkage through a semi-Bayesian approach, the occupational categories with the largest number of subjects remained associated with an increased OR, including painters, bricklayers, stonemasons and tile setters, bricklayers in construction industry, lorry and van drivers and laborers. As reported in Supporting Information Table S1, several occupations were associated with an OR of at least 2.0, including roofers (ISCO code: 953; OR: 2.04, 95% CI: 0.61–6.84, which decreased to 1.43 after SB adjustment), earth-moving and related machinery operators (ISCO: 974; OR: 2.12, 95% CI: 1.00–4.53, which decreased to 1.68 after SB adjustment), constructional steel erectors (ISCO: 87440; OR: 7.12, 95% CI: 0.86–59, which decreased to 1.56 after SB adjustment). Supporting Information Table S1 shows also that, apart from lorry and van drivers, none of the other types of drivers had an increased UADT cancer risk (the OR for motor vehicle drivers as a whole, ISCO code 985, was 1.00, 95% CI: 0.77–1.30). The four 3-digit ISCO occupational categories associated with an increased risk of UADT cancer in the main analyses (Table 2) were analyzed also in the Paris center. Risk of UADT cancer was increased among construction painters (ISCO code: 931; OR: 1.28, 95% CI: 0.54–3.02; 16 exposed cases) and bricklayers, stonemasons and tile setters (ISCO: 951, OR: 1.98, 95% CI: 1.01–3.87; 35 exposed cases), while the number of exposed subjects was too low to be analyzed for loggers (four exposed cases and 0 exposed controls) and electronic fitters (two exposed cases and two exposed controls).

Out of 172 industries evaluated (four digits, Supporting Information Table S2), we found an increased risk associated with a $p < 0.05$ in nine categories (Table 2) and a decreased risk ($p < 0.05$) in four categories. As summarized in Table 2, restriction of the analyses to subjects employed for at least 10 years increased most of the estimates, in particular for construction of motorways, roads, airfields and sport facilities (OR 5.61, 95% CI: 1.21–26.1; 15 exposed cases) and for cargo handling (OR: 4.85, 95% CI: 1.29–18.3; 14 exposed cases). Adjustment for educational level changed OR estimates more than marginally only for cattle and dairy farming industries. After semi-Bayesian shrinkage, cargo handling and categories related to the construction of buildings remained associated with an increased risk: Building of complete constructions or parts thereof, Civil engineering, not further specified, General construction of buildings and civil engineering works, Erection of roof covering and frames, Construction of motorways, roads, airfields and sport facilities. The SB adjustment decreased the OR associated with employment in the mining of uranium and thorium ores industry substantially from 9.4 to 1.5, as this category included only 10 subjects (nine of which came from the Prague centre). Among the industries associated with at least a two-fold increased risk, we found an OR of 2.56 (95% CI: 0.82–8.00) for workers in the manufacture of concrete products for construction purposes industry (NACE code: 2661), an OR of 2.33 (95% CI: 0.97–5.61) for manufacture of parts and accessories for motor vehicles and their engines (NACE: 3430) and an OR of 2.07 (95% CI: 0.58–7.34) for operation of dairies and cheese making (NACE: 1551) (Supporting Information Table S2). After SB adjustment all these OR estimates were below 1.5, with the exception of the manufacture of parts and accessories for motor vehicles and their engines industry which was associated with an OR of 1.59 (95% CI: 0.82–3.08).

Table 3 reports the results for the increased-risk occupations and industries by UADT cancer subtype. For most of the occupations and industries there was no marked variation in risk estimates. However, bricklayers and workers employed in the farming of cattle and dairy farming industry had an increased risk only of oral/oropharyngeal and esophageal cancer; the excess risks found for

workers in the mining of uranium and thorium ores as well as for drivers were specific for cancer of the hypopharynx/larynx; the risk associated with having worked as a painter was higher for oral/oropharyngeal cancer; loggers had an increased risk especially for hypopharyngeal/ laryngeal and esophageal cancer.
We also carried out a full analysis in each of the three UADT cancer subtypes, with results summarized in Supporting Information Tables S1 and S2. This approach increases dramatically the number of comparisons but some results are of interest for the interpretation of excess risks found in the main analyses. For example, consistently with the results reported in Table 3, workers in the painting and glazing industry (NACE code: 4544) had an increased risk of oral/oropharyngeal cancer (OR: 2.03, 95% CI: 1.03–3.99; 23 exposed cases) but not of cancer in the hypopharyx /larynx (OR: 0.96, 95% CI: 0.41–2.25; 12 cases).

Women

In total, 71 occupations (3 and 5 ISCO digits) and 44 industries (4 NACE digits) had at least 10 exposed subjects and were therefore retained for further analyses (Supporting Information Tables S3 and S4). Among these, employment in the retail sale of furniture, lighting equipment and household articles not elsewhere classified (Nace code: 5244) was the only category associated with an increased risk with a *p*-value <0.05 (OR: 3.53, 95% CI: 1.24–10.07; 12 exposed cases). Out of the 19 high-risk occupations and industries found in the analyses restricted to men, having worked as a laborer (ISCO code: 99910; tobacco- and alcohol-adjusted OR: 1.44; 95% CI: 0.68–3.03; 18 exposed cases), having been employed in the general construction of buildings and civil engineering works industry (NACE code: 4521, OR: 0.52; 95% CI: 0.16–1.73; 4 exposed cases) and having worked in the other retail sale in non-specialized stores industry (NACE code: 5212, OR: 1.97, 95% CI: 0.88–4.40; 16 exposed cases) included a sufficient number of subjects (at least 10) to be investigated.

Discussion

We studied occupational history in relation to UADT cancer risk in a large multicenter European study. Information on occupational history was obtained in a face-to-face interview using a standardized and detailed questionnaire, which was then coded by trained coders blinded to the case–control status of the subjects. We also had detailed information on the main potential confounders, namely tobacco and alcohol, which have been analyzed in *ad-hoc* papers.28
The assessment of exposure was based on standard coding of occupations and industries based on ISCO–NACE classification systems, implying that no direct information on specific carcinogens was available. Being an exploratory study assessing a large number of potential associations, there is the risk of false positive associations, as well as the possibility that some of the occupations and industries which were not associated with UADT cancer risk still entail exposure to UADT carcinogens. To evaluate the robustness of our positive findings, we used SB adjustment and conducted analyses restricted to occupations and industries in which subjects had worked for at least 10 years. Nevertheless, results should be interpreted with caution and discussed in the context of previous knowledge on occupational risk factors for UADT cancer. Selection and recall bias are other potential limitations of our study. Participation in the study was lower among controls than cases especially in the centers which used a population-based design. However, adjustment for educational level, typically one of the main determinants of participation, modified only marginally our estimates suggesting a limited role of selection bias. Although we cannot exclude the possibility of recall bias, occupational factors are not established causes of UADT cancer and it is therefore unlikely that cases reported their occupational history more accurately or in a biased fashion. Consistently, cases and controls reported a similar number of job periods (Table 1).
Some of our findings are consistent with previous studies on occupational factors for UADT cancer; these results should therefore be considered as supportive of previously reported associations, although in most of the cases the involved carcinogens are not know. We found an excess risk of

UADT cancer for some categories of construction workers, including reinforced concreters, bricklayers, constructional steel erectors, roofers and workers employed in the erection of roofs and frames, and those working in the construction of roads. Some of these risks increased in analyses restricted to long duration of employment and many of them remained elevated after SB adjustment. Bricklayers had an increased risk of oral/oropharyngeal and esophageal cancer but not of the laryngeal cancer. This is consistent with recent results from a comprehensive register-based study carried out in Nordic countries25 that found a 30–40% increased risk for cancer of the oral cavity (87 exposed cases) and the pharynx (115 cases), while relative risks of 1.11 for esophageal cancer (180 cases) and 1.05 for laryngeal cancer (167 cases). Two previous studies on laryngeal cancer that investigated bricklayers separately (with about 50 exposed cases each) found relative risks of 1.0314 and 1.6.13

The IARC international cohort on asphalt workers34 and a recent update limited to the German part of that cohort35 reported an increased risk of UADT cancer which is consistent with our findings for workers in the erection of roofs and construction of roads, although results from the cohort study were not adjusted for smoking and alcohol and the increased risk was mainly due to the German data. There is little information on roofers and pavers from previous case–control studies, with the exceptions of two studies on laryngeal cancer reporting a relative risk of 0.4, based on five exposed cases,13 and a relative risk of 6.4 based on 22 exposed cases.11

The evidence on the risk of UADT cancer among concrete workers is more convincing. In particular, our finding of an increased risk for reinforced concreters is consistent with similar findings from two previous case–control studies on laryngeal cancer13, 14 and an increased risk in the concrete and cement manufacture industry found in another case–control study on laryngeal cancer.20 Some studies report an association between exposure to cement dust, which is a complex and heterogeneous mixture, and cancer of the larynx36 or pharynx,37 although other studies did not replicate this association.20, 27

Apart from specific exposure to cement dust in concrete workers, employment in the different types of construction jobs that we found at increased risk of UADT cancer involves exposure to a number of agents which have been previously reported to be associated with at least one of the different UADT subtypes, including asbestos, polycyclic aromatic hydrocarbons, inorganic dusts and solvents.26, 27

The excess risk for painters found in our study remained after SB-adjustment while it did not increase with increasing duration of employment. The risk was evident mainly for oral/oropharyngeal cancer. Several studies have investigated UADT cancer risk, especially laryngeal cancer, in association with having worked as a painter, finding moderately increased risks.9–14, 19, 21, 22, 24 Similarly, some cohort studies found increased risk of a small magnitude for cancers of the pharynx or oral cavity.25, 38–40 A recent IARC monograph has summarized the epidemiological evidence for cancer risk in painters, including the risk of UADT cancer.40 The working group concluded that, although data were insufficient for evaluation, there was some consistency between case–control and cohort studies for an increased risk of cancers of the pharynx and esophagus. Painters are or were exposed to a great number of chemical compounds, including organic and inorganic solvents, chromium, pigments, additives, binders as well as silica and asbestos and it is thus difficult to speculate on possible specific UADT carcinogens which could explain the association.40

The risk of laryngeal cancer that we found among uranium miners was entirely due to one of the participating centers, namely the city of Prague that has uranium mines in its vicinity. The collaborative analysis of cohort studies of underground miners exposed to radon published in 199541 and some more recent analyses of cohorts of uranium miners42, 43 found a slightly increased risk of laryngeal cancer of about 20%.44

Drivers have been found to have an increased risk of UADT cancer in a number of studies although there is marked inconsistency.12, 14, 15, 21, 23–25 In our study the risk was increased for lorry and van drivers as well as for earth-moving and related machinery operators but not for drivers as a whole. The increased risk among loggers observed in the present study has been found before in a large case–control study on laryngeal cancer.14 However, in the recent register-based study in the Nordic countries, the incidence of each UADT cancer type was decreased among forestry workers compared with the general population.25 Laborers, as well as dockers, have been noted to have an increased UADT cancer risk in a number of studies but these categories are rather heterogeneous.9, 11, 13–16, 18, 19

The increased risk that we found among workers employed in the cattle and dairy farming industries is a new association and should then be treated with a greater degree of caution. The association was slightly attenuated after adjustment for educational level. As shown in the Supporting Information Tables S1 and S2, an increased risk of UADT cancer was also found among workers employed in the operation of dairies and cheese making industry (NACE: 1551, OR: 2.07) and for dairy farm workers (ISCO 625, OR: 1.75) and dairy product processors (ISCO 775, OR: 1.83). Most, if not all, previous studies on UADT cancer did not analyze dairy workers separately. In a Finnish cohort study on cancer risk among food industry workers, the risk was increased by 30% for laryngeal cancer (three cases) and by 100% for esophageal cancer (three cases).45 Cohort studies of farmers including a large proportion of diary farmers do not reveal an increased risk of UADT cancer.46–48

There is little information on occupational risk factors for UADT cancer in women. Our study included almost 400 female cases and a previous case–control study on UADT cancer22 included 350 women but prevalences of exposure were low and neither study found a clear evidence of an increased risk associated with specific occupations or industries.

In conclusion, this large European study provides evidence that occupational exposures play a role in UADT cancer etiology and contribute to explain, together with alcohol, smoking and diet, socioeconomic differences typically observed in UADT cancer risk.6 The most internally consistent findings, also supported by previous studies, were obtained some specific workers employed in the construction industry, including reinforced concreters, bricklayers, painters and workers employed in the construction of roads or the erection of roofs.

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