Occupations and the Risk of Head and Neck Cancer: A Pooled Analysis of the International Head and Neck Cancer Epidemiology (INHANCE) Consortium

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Khetan, Prerna MPH; Boffetta, Paolo MD; Luce, Daniele PhD; Stucker, Isabelle PhD; Curado, Maria Paula PhD; Menezes, Ana PhD; Wunsch-Filho, Victor PhD; Ahrens, Wolfgang PhD; Lagiou, Pagona MD; Serraino, Diego PhD; Richiardi, Lorenzo PhD; Kjaerheim, Kristina PhD; Conway, David PhD; Thomson, Peter MD; Muscat, Joshua PhD; Mates, Dana PhD; Ramroth, Heribert PhD; Menvielle, Gwenn PhD; Vaughan, Thomas L. MD; Brenner, Hermann MD; Lee, Yuan-Chin Amy PhD; La Vecchia, Carlo PhD; Hashibe, Mia PhD; Hashim, Dana MD

The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York City, New York (Dr Khetan, Dr Boffetta, Dr Hashim); University of Rennes, National Institute of Health and Medical Research, School of Advanced Studies in Public Health, Institute for Health, Environment and Work Research - Research Unit UMR_S 1085, Pointe-a-Pitre, France (Dr Luce); Cancer and Environment Team, National Institute of Health and Medical Research U1018, Paris-Sud University, Paris-Saclay University, Villejuif, France (Dr Stucker); Cancer and Environment team (CESP), (Inserm) National Institute of Health and Medical Research U1018, Paris-Sud University, Paris-Saclay University, Villejuif, France (Dr Stucker); Federal University of Pelotas, Pelotas (Dr Menezes); University of Sao Paulo, Sao Paulo, Brazil (Dr Wunsch-Filho); Leibniz Institute for Prevention Research and Epidemiology, Bremen Institute for Prevention Research and Social Medicine , Bremen, Germany (Dr Ahrens); School of Medicine, National and Kapodistrian University of Athens, Greece (Dr Lagiou); Oncological Reference Center, Institute of Scientific Characterization and Hospitalization, Aviano, Italy (Dr Serraino); Department of Medical Sciences, University of Turin, Turin (Dr Richiardi); Cancer Registry of Norway, Institute of Population-based Cancer Research, Oslo, Norway (Dr Kjaerheim); School of Medicine, Dentistry, and Nursing, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK (Dr Conway); University of Hong Kong, Hong Kong, China (Dr Thomson); Penn State College of Medicine, Hershey, Pennsylvania (Dr Muscat); National Institute of Public Health, Bucharest, Romania (Dr Mates); University of Heidelberg (Dr Ramroth); National Institute of Health and Medical Research, Sorbonne University, Pierre Louis Institute of Epidemiology and Public Health, Paris, France (Dr Menvielle); Fred Hutchinson Cancer Research Center, Seattle, Washington (Dr Vaughan); Division of Clinical Epidemiology and Aging Research, German Cancer Research Center, Heidelberg, Germany (Dr Brenner); Division of Preventive Oncology, German Cancer Research Center and National Center for Tumor Diseases, Heidelberg, Germany (Dr Brenner); German Cancer Consortium, German Cancer Research Center, Heidelberg, Germany Hermann Brenner (Dr Brenner); Division of Public Health, Department of Family & Preventive Medicine and Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City, Utah (Dr Lee, Dr Hashibe); Department of Clinical Sciences and Community Health, University of Milan, Milan (Dr La Vecchia), Italy.

Address correspondence to: Prerna Khetan, MPH, Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Pl, New York, NY 10029 (prernakhetan13@gmail.com).

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Abstract

Objective: To investigate the associations between head and neck cancer (HNC) risk and occupations.

Methods: We harmonized data on occupations in a pooled analysis of 8839 HNC cases and 13,730 controls in International Head and Neck Cancer Epidemiology (INHANCE) consortium. Logistic regression was used to estimate odds ratios (ORs) for associations of occupations and HNC risk. Population attributable fraction (PAF) for occupations was calculated using the formula P_{EC} x (OR - 1)/OR [1].

Results: Trend of increasing HNC risk was found with increasing duration of employment for many occupations, including cooks (OR = 1.36; 95% confidence interval [CI] 1.09 to 1.68), cleaners (OR = 1.38; 95% CI 1.13 to 1.69), painters (OR = 1.82; 95% CI 1.42 to 2.35). The PAF for a priori occupations was 14.5% (95% CI 7.1% to 21.9%) for HNC.

Conclusions: We found associations between certain occupations and HNC risks, including for subsites, with a duration-response relationship.

Head and neck cancer (HNC) accounts for more than 550,000 cases and 380,000 deaths annually, worldwide [2]. HNC includes cancers originating in the oral cavity, the oropharynx, the hypopharynx, and the larynx. The majority of HNC cases are preventable by limiting exposure to risk factors [3]. Tobacco use, alcohol consumption, human papillomavirus (HPV) infection, and a diet poor in fruits and vegetables are the primary risk factors known to be associated with HNC [4].

In addition to these major risk factors, several occupational exposures are recognized risk factors for some HNC sites (asbestos and strong acids for larynx; leather dust, and wood dust for sinonasal cancer) and suspected to be risk factors for other cancers of the head and neck. According to the International Agency for Cancer Research (IARC), all forms of asbestos are carcinogenic to humans (Group 1) [5]. They had observed positive associations between exposure to asbestos and cancer of the pharynx, stomach, and colorectum [5]. IARC had also classified wood and leather dust as type 1carcinogens, with enough evidence to establish a causal link between these materials and cancer. In particular, these were considered causal for cancers of the nasal cavity and paranasal sinus [6]. However, the relationship of these exposures with other cancers of head and neck, especially oral and pharyngeal cancers, has been sparsely studied due to small sample sizes [6]. Several toxic

metals and inorganic compounds including nickel, cobalt, lead, vanadium, beryllium, arsenic, and chromium are also considered by IARC to be definite or probable carcinogens [7-10]. Thus, occupations involving these exposures were associated with the risk of developing head and neck cancer.

Specific to HNC, occupational or environmental toxins have been investigated for a potential role in carcinogenesis. However, previous epidemiological studies had small sample size to study the association of occupations by HNC subsites and inadequate adjustment for the potential confounding by tobacco smoking, alcohol drinking, race, study, geographical region, education, and sex [11]. This is a study to determine the associations between occupations and HNC with higher power, while adjusting for potential confounders. We pooled occupations and HNC data from studies participating in the international head and neck cancer epidemiology (INHANCE) consortium and studied occupations which have shown limited evidence in previous studies to be associated with HNC risk [12-15] and entailed exposure to agents which were identified by IARC as known or suspected carcinogens [16,17].

MATERIALS AND METHODS

Studies and Participants

The INHANCE consortium is a collaboration of research groups leading studies of HNC to improve the understanding of the causes and mechanisms of HNC. For the purpose of this analysis, we selected 12 case-control studies [1,18] with comparable data on occupations out of the 16 studies which had information on occupations. Six of the selected studies were from Europe, four from North America, and two from Latin America. Four studies which were excluded were Seattle (1985 to 1995), Los Angeles, Boston, and Rome. The reason for excluding them was large number of missing data on occupations: Los Angeles (37.2% missing), Boston (69.3% missing), Rome (63.5% missing). Seattle (1985 to 1995) was excluded because we did not have necessary information on the coding system used for the occupations in that study (see Table, Supplemental Digital Content 1, http://links.lww.com/JOM/A516, which details on the individual studies). Some of these data were partially analyzed and published in previous studies [12-14,19]. The methods used for questionnaire harmonization and pooling of data have been described previously [1,18]. This pooled analysis included 12,214 incident HNC cases and 14,255 controls. Incident cases consisted of patients with invasive tumors of the head and neck (n = 8839), including oral cavity (n = 1859), oropharynx (n = 1,513), hypopharynx (n = 991), larynx (n = 3848), and oral cavity/pharynx not otherwise specified (n = 2515), as defined by International Classification of Disease, 2nd edition (ICD-O2) or ICD 9th or 10th edition [1]. We excluded participants with missing information on age (n = 204), sex (n = 253), or occupation (n = 3,852), leaving 8839 cases and 13,730 controls in the analysis. Written informed consent was obtained from study subjects, and approvals were obtained by the institutional review board at each institution involved [15].

Harmonization of Occupations

The occupations were chosen, a priori (see list, Supplemental Digital Content 2, http://links.lww.com/JOM/A517, which shows the occupations under consideration in our study). Studies had their occupations coded according to International Standard Classification of Occupations (ISCO) codes. It was possible to convert them all to International Standard Classification of Occupations-1968 version and were then able to harmonize them.

Covariates

We considered age (5-year categories), sex, race/ethnicity (White, Black, Hispanic, Asian and

Pacific Islander, Brazilian, and other), study, geographic region (Europe, North America, South or Central America), and education level (no education, junior high school, some high school, high school graduate, technical school, college graduate, depending on country). Cumulative tobacco smoking was categorized as those who smoked 0 to 10.0, 10.1 to 20.0, 20.1 to 30.0, 30.1 to 40.0, 40.1 to 50.0, and 50.0+ pack-years [20]. Alcohol consumption was calculated as the number of drinks/d based on average cumulative lifetime consumption, assuming one standardized drink contains 15.6 mL of pure ethanol (never drinker, 0.1 to 0.9, 1.0 to 2.9, 3.0 to 4.9, and 5.0+) [1]. We included missing data on race/ethnicity (0.06%), tobacco smoking (8.19%), and alcohol drinking (3.83%) in separate categories.

Statistical Analysis

We used frequency distribution analysis to describe our data. Multivariable logistic regression models were used to estimate odds ratios (ORs) and corresponding 95% confidence intervals (95% CI) for associations between occupations and incident HNC. We first studied broad occupation categories defined by two-digit ISCO-68 codes and then, specific occupations defined by three-digit ISCO-68 codes. We used a dichotomous variable "ever having worked in a given occupation under our study" versus "never having worked in all the occupations under our study" to determine the association. We chose this unique group as our reference because we wanted to investigate the association of specific occupations with HNC verses those who have never been exposed to any of the a priori suspected occupational carcinogen through those occupations. In this way we tried to keep the occupational carcinogen exposure in the reference group to its minimum. The risk estimates of the various occupations selected for the analysis were directly comparable. P-values were adjusted for multiple hypothesis testing (P') (because we are testing multiple occupations) according to the Ryan-Holm step-down Bonferroni method (controlling for familywise error rate) and dependent false discovery rate method (controlling for false discovery rate) [21]. The 2-sided P or P' <=0.05 was considered statistically significant. Subsequent analyses focused on the occupations for which P-value on multiple hypothesis adjustment was <=0.05. We studied the relationship to duration of employment (<=10 years vs >10 years). Tests for linear trend were conducted using duration of employment as a continuous variable. For the analysis including duration of employment, data were contributed by all studies except New York Multicenter. ORs were also estimated separately by cancer subsite. All ORs were adjusted for age, sex, race, education, study, geographical region, alcohol consumption, and tobacco smoking. To test the robustness of our findings, we conducted sensitivity analyses excluding alcohol drinking in one model, tobacco smoking in another model, and both alcohol drinking and tobacco smoking in a third model. For each occupation category (two-digit), we also assessed potential interactions with smoking, alcohol drinking by including cross-product terms in the models. Smoking and drinking were introduced as categorical variable with many categories. The population attributable fraction (PAF) for occupations was calculated using the formula P_{EC} x (OR - 1)/OR^1, where OR is the adjusted OR and P_{EC} is the proportion of cases exposed to any of the a priori occupations in our study. For the calculation of PAF, we included all the occupations under our study irrespective of their significant or insignificant findings in our study. Harmonization of occupations and data analysis were done using the SAS Statistical Software (Version 9.4, SAS Institute Inc., Cary, NC).

RESULTS

87.5% of cases and 61.2% of controls were ever smokers. 87.3% of cases and 77.8% of controls consumed alcohol (see Table, Supplemental Digital Content 3, http://links.lww.com/JOM/A518, which reports descriptive characteristics of cases and controls).

We first considered broad categories of occupations (ie, two-digit ISCO code) and HNC. Significantly increased ORs were observed for many service workers and production and related workers, transport equipment operators, and laborers. ORs and 95% CIs are presented by two-digit broad ISCO-68 occupational categories in Table 1.

To understand the role of more specific occupations in HNCs, results of the analyses by duration of employment and respective three-digit ISCO code occupation categories are presented in Table 2. The table reports occupations which showed significantly increased overall OR together with significant trend test. Occupations for which number of both exposed cases and exposed controls were greater than 100 with overall significant OR even with insignificant trend test are also reported (see Table, Supplemental Digital Content 4, http://links.lww.com/JOM/A519, which reports complete results for analyses by duration of employment).

Increased ORs, with significant trend in risk with increasing duration of employment were observed for the majority of occupations we studied under groups service workers and production and related workers, transport equipment operators, and laborers. A positive association, without trend in risk with increasing duration of employment, was observed for few production and related workers: machine-tool operators (OR = 1.37; 95% CI 1.1 to 1.7), blacksmiths, toolmakers and machine-tool operators (OR = 1.28; 95% CI 1.01 to 1.63), painters not elsewhere classified (OR = 1.36; 95% CI 1 to 1.85), and some construction occupations.

HNC risk by selected occupation categories (three-digit ISCO code) for subsites are reported in Tables 3 and 4 (see Table, Supplemental Digital Content 5, http://links.lww.com/JOM/A520, which presents complete results for analysis by subsites). The ORs were consistently increased for larynx for most of the occupations we studied. Motor vehicle mechanics (OR = 1.41; 95% CI 1.11 to 1.78), motor vehicle drivers (OR = 1.22; 95% CI 1.04 to 1.44), cleaners (OR = 1.56; 95% CI 1.2 to 2.03), and few occupations involving handling and producing textile showed significantly increased ORs only for larynx. Waiters, bartenders showed increased ORs for oral cavity (OR = 1.67; 95% CI 1.13 to 2.48) and larynx (OR = 1.44; 95% CI 1.09 to 1.9). Plumbers, pipe fitters, structural metal preparers, and erectors showed significantly increased ORs for all subsites except larynx. Butchers and meat preparers, material-handling equipment operators showed significantly increased ORs for oral cavity, pharynx, and oropharynx.

In a sensitivity analysis to assess the impact of confounding by smoking and drinking on HNC risks,1 we found that after excluding alcohol drinking and tobacco smoking from the regression models, there was increased risk of HNC for service workers: launderers, dry-cleaners, and protective service workers; production and related workers: wood preparation workers and paper makers, cabinetmakers and related woodworkers, rubber and plastics product makers. All ORs were in the order of 1.5 (see Table, Supplemental Digital Content 6, http://links.lww.com/JOM/A521, which shows confounding by smoking and drinking). This shows that the relationship between certain occupations and HNC may be largely explained by confounding by smoking and drinking.

We observed interactions between building caretakers, charworkers, cleaners, and both tobacco smoking and alcohol drinking. Protective service workers showed interaction with alcohol drinking only. Cooks, waiters, bartenders and tailors, dressmakers, sewers, upholsterers showed interaction with tobacco smoking. These associations are magnified by smoking and drinking (data not shown).

Approximately 14.5% (95% CI 7.1% to 21.9%) of head and neck cancer in this study would have been prevented if the at-risk occupations associated with HNC were eliminated, assuming a causal relationship.

DISCUSSION

In this large, pooled analysis of occupations in relation to HNC, we found elevated risks for several occupational categories. These associations were based on a large sample size and on models

including adjustment for main confounders, and risks increased with duration of employment. Many of these associations remained significant after adjusting for multiple hypothesis testing. Laryngeal cancer in particular, had the highest and most consistent elevated risk patterns, suggesting an inhalation route of exposure.

The large number of positive associations is not surprising since these occupations were selected on the basis of the findings of previous studies. In this respect, our study should be seen mainly as hypothesis-testing rather than hypothesis-generating.

The mechanism by which chemical carcinogens may cause HNC development is likely to be through a multistep process [22]. Similar to many other cancers, it is initiated by repeated insults to the normal epithelium by carcinogens including tobacco, alcohol, and some occupational factors [22]. Though the precise mechanism of action of occupational carcinogens is not known, it is likely that several steps (eg, DNA damage, epigenetic changes, chronic inflammation) are involved following exposure to different agents.

We found that the larynx is the cancer site most consistently associated with the occupations we studied. This suggests that the associated occupations may involve exposures which have a detrimental impact on the upper respiratory tract [23]. We observed positive association for painters, construction with laryngeal cancer in our study. IARC has already classified occupational exposures in painting as Group 1 lung carcinogens, supporting a carcinogenic effect on the respiratory tract. In addition, our findings also provide evidence of an association between painters, construction, and oral cavity and pharyngeal cancer, suggesting an impact on the digestive tract and an ingestion route of exposure. These associations had been inconclusive in previous studies [24]. This analysis by subsite helped assess etiological differences in terms of specific agents for HNC. The possible mechanism may be similar to what has been observed for exposure to asbestos and welding fumes [14] through inhalation and to a lesser extent ingestion at the workplace environment. The mechanisms of carcinogenicity of asbestos fibers are not know with certainty but they are likely to involve generation of free radicals that directly cause genotoxicity, interference with the mitotic process, activation of macrophage and continuous inflammation producing reactive nitrogen and oxygen species resulting in epigenetic alterations, genotoxicity, and tissue injury [5]

The results of the analysis combining occupations with duration of employment are consistent with the previous observations that employment duration plays a role in HNC development and support a causal interpretation of the findings. We observed increased risks of HNC with significant trend in risk with increasing duration of employment for the majority of occupations we studied, like plumbers and pipe fitters, welders and flame-cutters similar to previous studies [5,14,25,22,23] possibly due to exposure to asbestos and welding fumes through inhalation and ingestion. A duration-response relationship was also reported [14]. The mechanism by which welding fumes cause development of cancer is thought to be through induction of chronic inflammation and immunosuppression [26].

We found interaction in our data which shows that occupational exposure to various deleterious agents may facilitate the penetration of other carcinogens (through tobacco smoking or alcohol drinking) in the mucosa and vice-versa, resulting in elevated risks of HNCs. In our population, HNC occurred more often if smoking and having an occupation with exposure to inhalation of engine exhausts, textile dusts, cleaning agents, and solvents occurred concurrently. Although smoking is a primary risk factor for HNCs due to exposure to already established human carcinogens, most studies done until today had limited statistical power to study interaction.

Our study showed that approximately 14.5% of the cases of head and neck cancer were attributable to occupations under our study. Previous studies have already shown that among the never drinkers, 24% (95% CI 16% to 31%) of the cases of head and neck cancer were attributable to ever cigarette smoking [1]. Among the never users of tobacco, 7% (95% CI 4% to 16%) of the cases of head and neck cancer were attributable to alcohol drinking [1]. This shows that occupational factors are

weaker risk factors for HNC than smoking.

We found elevated risks for waiters, bartenders and related workers. Such finding has also been reported in several studies [13,14,27-34] and could be explained by the exposure to passive smoking (both mainstream smoke and sidestream smoke). Previous studies have shown that involuntary smoking carcinogens are metabolized by passive smokers and can increase HNC risk [34,35].

Elevated risks for butchers and meat preparers were also found in our study. Previous studies have already shown elevated risk for them [14,31,36,37]. This could be explained by their exposure to viral agents, nitrosamines, or polycyclic aromatic hydrocarbons.

The study found elevated risk for dockers and freight handlers, crane and hoist operators, earth-moving, and related machinery operators. Increased risks in these occupations have been previously reported [13,14,28,38] This might be explained by their exposure to engine exhausts, materials they load or transport.

Reinforced-concreters, cement finishers and terrazzo workers, roofers, carpenters, joiners and parquetry workers, plasterers showed positive association similar to many previous studies [13,14,27,29,31,32,34,38,39]. A plausible explanation for these associations might be the exposure to asbestos, silica, man-made vitreous fibers, and cement dust.

We found high OR for spinners, winders, weavers, knitters, similar to previous studies [17,40]. The mechanisms involved in the process may be chronic irritation of the mucosa by textile dusts, an exposure to nickel compounds, cadmium compounds, chromium compounds, lubricating oils, acrylonitrile, and asbestos [17]. According to IARC, working in the textile manufacturing industry involves exposures that are possibly carcinogenic to humans [41].

We observed that occupations that are strongly associated with higher risks of HNC are service workers including cooks, waiters, bartenders, cleaners; production and related workers including butchers and meat preparers, occupations involving work with metal and machinery, occupations involving handling and producing textile, carpenters and other construction workers painters, construction, material-handling and related equipment operators, dockers and freight handlers, transport equipment operators: motor vehicle drivers and laborers. The association for HNC and protective service workers, cabinetmakers and related woodworkers, rubber and plastics product makers, launderers, dry-cleaners, wood preparation workers, and paper makers, is likely due to strong confounding effect of smoking and drinking behavior in these occupations.

Potential limitations of this study include the possibility of recall bias, as with any observational retrospective study. However, this is unlikely to be based on case/control status as occupational exposures as causes of HNC are not well known in general population. Another limitation is that we could not analyze occupations at the 5-digit level (or most specific occupation level). This was due to the coding system we used to harmonize the occupational data. Updated ISCO-68 coding system classifies occupations upto three-digit level and it does not detail up to the five-digit level. Another limitation is that we do not have industrial data to study the association with HNC. Additionally, we could not study exposures in particular occupations as we did not have data on exposure agents. Lastly, we do not have information regarding frequency or intensity of each occupational exposure, although we used duration of employment at each exposed occupation as a surrogate for dose [7].

There are several strengths of this study. First, it included a large sample size which provided adequate statistical power to detect associations between major occupational groups and allowed analyses by cancer subsites. Second, external validity of the study is strengthened by inclusion of three different geographic regions (sensitivity analysis did not show any significant findings-data not shown). Third, we adjusted for multiple hypotheses testing to control the Type 1 error rate and last, the analyses by duration of employment reinforced the associations which we found in our study.

In conclusion, this study shows potential risks for HNC subsites from occupational factors, with dose-response analyses according to duration of employment and simultaneous exposure to cofactors like tobacco and alcohol. It is important to stress that elimination of occupational factors by taking correct precautions at work place may reduce the risk of HNC. The identification of specific occupations that are associated with HNC could inform occupational health policy and potentially reduce the HNC burden. Further studies on specific exposure agents needs to be done.

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