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Laryngeal Cancer Risks in Workers Exposed to Lung Carcinogens: Exposure–Effect Analyses Using a Quantitative Job Exposure Matrix

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Abstract

Introduction

Various established occupational lung carcinogens are also suspected risk factors for laryngeal cancer. However, individual studies are often inadequate in size to investigate this relatively rare outcome. Other limitations include imprecise exposure assessment and inadequate adjustment for confounders.

Methods

This study applied a quantitative job exposure matrix (SYN-JEM) for four established occupational lung carcinogens to five case–control studies within the INHANCE Consortium. We used occupational histories for 2256 laryngeal cancer cases and 7857 controls recruited from 1989-2007. We assigned quantitative exposure levels for asbestos, respirable crystalline silica, chromium-VI, and chromium-VI & nickel combined (to address highly correlated exposures) via SYN-JEM. We assessed effects of occupational exposure on cancer risk for males (asbestos, respirable crystalline silica, chromium-VI, chromium-VI & nickel) and females (asbestos, respirable crystalline silica), adjusting for age, study, tobacco smoking, alcohol consumption, and asbestos exposure where relevant.

Results

Among females, odds ratios (ORs) were increased for ever versus never exposed. Among males, p-values for linear trend were <0.05 for estimated cumulative exposure (all agents) and <0.05 for exposure duration (respirable crystalline silica, chromium-VI, and chromium-VI & nickel); strongest associations were for asbestos at >90%ile cumulative exposure (OR=1.3, CI=1.0-1.6), respirable crystalline silica at 30+ years duration (OR=1.4, CI=1.2-1.7) and 75%-90%ile cumulative exposure (OR=1.4, CI=1.1-1.8), chromium-VI at >75%ile cumulative exposure (OR=1.9, CI=1.2-3.0), and chromium-VI & nickel at 20-29 years duration (OR=1.5, CI=1.1-2.2).

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Conclusions

These findings support hypotheses of causal links between four lung carcinogens (asbestos, respirable crystalline silica, chromium-VI, and nickel) and laryngeal cancer.

Keywords

Occupational Exposure, Laryngeal Neoplasms, Case–control Studies, Asbestos, Respirable Crystalline Silica, Nickel, Chromium(VI)

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INTRODUCTION

An estimated 177,000 people worldwide receive a diagnosis of laryngeal cancer each year (1). Smoking and alcohol are presumed to be responsible for a large proportion of these cancers (2); asbestos and strong inorganic acid mists are the only other agents with established causal links to laryngeal cancer in humans (3,4). A growing body of evidence indicates that other occupational exposures may play a role in the development of laryngeal cancer; however, individual studies are often inadequate to assess relationships with this relatively rare outcome. Exposure assessment with low accuracy is an important limitation in this regard, in addition to small study size and inadequate adjustment for potentially strong confounders (i.e., smoking and alcohol consumption) (5).

Population-based case–control studies can be a useful approach when the outcome of interest, such as laryngeal cancer, is rare. Exposure assessment in this context, complicated by participants' employment in a wide variety of occupations and industries, often consists of retrospective estimation using some combination of self-reporting, expert judgment, and/or generic job exposure matrices (JEMs) to assign exposures in a qualitative or semi-quantitative way (6).

While detailed exposure monitoring is typically not an option in case–control studies, relevant historical measurements can be integrated with occupational hygiene expertise to conduct quantitative exposure estimation through modeling. One example is the SYN-JEM (7), a quantitative job exposure matrix of established lung carcinogens based on personal measurements from 18 European countries and Canada. Although originally developed for use in a pooled analysis of lung cancer case–control studies (8), SYN-JEM can also be applied to retrospectively estimate occupational exposure to these agents for other health outcomes in community-based studies.

The International Agency for Research on Cancer (IARC)'s Monographs Program has classified asbestos, crystalline silica dust, chromium VI compounds, and nickel compounds as Group 1 (Carcinogenic to humans) (3). These classifications were based in whole or in part on sufficient evidence in humans for cancer of the lung. Of these, asbestos is the only agent with sufficient

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evidence for a causal link with cancer of the larynx (limited evidence has not yet been established for the others, by the IARC classification). Further consideration of these agents as risk factors for laryngeal cancer is justified, given their established carcinogenic effects in the lung and common route of exposure via inhalation. The current study was conducted to investigate these relationships while addressing important quality issues (such as limited exposure assessment, study size, and control of confounding) in individual case–control studies of occupational exposure and laryngeal cancer.

METHODS

Study population

We drew the study population from the International Head and Neck Cancer Epidemiology (INHANCE) Consortium, a global collaboration established in 2004 among research groups currently or recently conducting large molecular epidemiologic studies of head and neck cancer (9). All studies included in the current analyses were required to have a recruitment protocol for cases and controls, as well as a structured questionnaire to collect information on demographic factors, occupational history, tumor characteristics, alcohol consumption, and tobacco use. Occupational histories consisted of a list of employment periods for each study participant over the course of their career, with start and end date as well as job held recorded for each period. Laryngeal cancer cases were classified by the original studies as participants with invasive tumors of the larynx (including glottis, supraglottis, and subglottis; ICD-10 codes C32.0-C32.3 and C32.8-C32.9) (9). Data were sent to the INHANCE Consortium with personal identifiers removed; we then carefully conducted harmonization procedures to ensure accuracy and consistency between studies, with all items double-checked for illogical or missing values and inconsistencies resolved via queries to original study investigators (10).

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To permit linkage with the SYN-JEM, the study sample was restricted to five INHANCE studies with occupational histories coded to the International Standard Classification of Occupations (ISCO)-68 of the International Labor Organization (11) (2469 laryngeal cancer cases and 8328 controls). Characteristics of the five case–control studies included in these analyses (after exclusions) are provided in eTable 1; http://links.lww.com/EDE/B599. Two were multicenter studies, based in Western Europe (12) and Latin America (13), respectively; the others were based in France (2 studies; (14,15)) and in Germany (1 study; (16)). Most studies were hospital-based; controls were all frequency-matched to cases on age, sex, and other factors. Participation rates ranged from 80%-96% for cases, and from 62%-86% for controls.

Ethics approval

Each INHANCE study obtained investigation approval from its respective institutional review board, and informed consent was obtained from every study participant. Approval for the current project was obtained from the IARC ethics committee (project 18-02).

Exposure assessment

Details on the development of SYN-JEM have been published elsewhere (7). In brief, empirical models were developed using individual personal measurements of occupational exposures in a range of European countries and Canada, collected between the 1970s and 2009 (17). Only measurements with a job code available and a sampling duration between 60 and 600 minutes were selected to construct a linear mixed-effects model for each agent (27,958 measurements for asbestos, 24,150 for chromium (of which 8363 were chromium-VI), 23,640 for respirable crystalline silica, and 22,081 for nickel).

Random effects terms included region/country and job title; fixed effects included measurement year, sampling duration, and prior exposure rating that was based on an independent general population job exposure matrix (DOM-JEM) that assigned no, low, or high exposure to all ISCO-68 job titles (18). Additional fixed effects that considered sampling and analytical aspects were selected

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for each agent as appropriate, such as "chromium type" to normalize all estimates to chromium-VI levels, and country-specific year of asbestos ban implementation to indicate whether the measurement was taken pre- or post-ban. Model predictions provided an estimated annual geometric mean exposure for a given job, region/country, and year for each agent, with asbestos expressed as f/ml, and respirable crystalline silica, chromium-VI, and nickel expressed as mg/m^3. Agent-specific overall linear time trends were applied to all jobs and regions for each agent.

The quantitative SYN-JEM estimates were linked with individual job periods from INHANCE self-reported occupational histories at Utrecht University's Institute for Risk Assessment Sciences. The SYN-JEM assesses exposure levels for each job title coded with the ISCO-68 (11). When exposure measurements were available, jobs classified as exposed by the DOM-JEM were assigned the job-specific estimates derived from the prediction model. In situations where there were fewer than five measurements for a job title, the job-specific estimate was calculated using the weighted mean of the jobs at the 5-digit ISCO-68 code within the same (3-digit) unit or (2-digit) group (19). For jobs considered unexposed in DOM-JEM, overrides were applied to SYN-JEM model predictions to assign zero exposure.

In the INHANCE data, over 99% of participants who had ever been estimated as exposed to nickel had also been exposed to Chromium-VI, with highly correlated exposure durations and cumulative exposures noted between the two agents ($r > 0.80$). Therefore, we assessed participants exposed to chromium-VI only (n = 446; 23% of all chromium-VI exposed participants) separately from participants co-exposed to both chromium and nickel. For the chromium-VI & nickel co-exposed group, we standardized exposures to each metal to the median exposure of the exposed group by dividing the estimated exposure of an individual by the group median for each of the two agents and then summing these two values. For example, an individual with 10 mg/m^3–years of chromium-VI (with group median of 2 mg/m^3–years) and 10 mg/m^3–years of nickel (with group median of 1 mg/m^3–years), would be assigned a standardized cumulative exposure of 15 unit years. We did this

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to address the issue of co-exposure while avoiding the assumption that chromium-VI and nickel have the same impact on laryngeal cancer odds ratios per mg/m^3-year, which would have been implied if these exposures were simply summed without standardization.

Statistical analyses

We fitted logistic regression models for males and females separately to assess the effects of exposure to asbestos, to respirable crystalline silica, to chromium-VI only, and to the combination of chromium-VI and nickel on laryngeal cancer. For females, we only assessed exposures to asbestos and respirable crystalline silica because of the small numbers of study participants exposed to chromium-VI and nickel.

Never exposed to the agent under evaluation formed the reference category for each analysis. For males, we assessed three exposure metrics for each agent: ever occupational exposure, duration of exposure (<10, 10-19, 20-29, and ≥30 years), and estimated cumulative exposure (summed over participants' entire work histories). For the cumulative metric, categorical cut-points were based on the exposure distribution among control participants: <50th, 50-75th, and >75th percentiles for chromium-VI and chromium-VI & nickel, and, where greater numbers of exposed participants were available, <50th, 50-75th, 75-90th, and >90th percentiles for asbestos and respirable crystalline silica. For females, the same exposure metrics were assessed, although median exposure in controls was used as the cut-point for categories of duration and cumulative exposure due to the small numbers of exposed participants.

We adjusted for potential confounders in stages. Model 1 estimates were adjusted for participant age and study (to account for differences in individual study time periods and methodologies used; see eTable 1; http://links.lww.com/EDE/B599). Model 2 estimates were additionally adjusted for tobacco smoking and alcohol consumption, since these are known risk factors for laryngeal cancer (2,10) and may be associated with occupational characteristics (20,21). Confounding by smoking is often adjusted for using pack–years (10,22–25); however, smoking cessation has also shown a strong

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negative association with laryngeal cancer, with risk decreasing as time since quitting increases (26). Therefore, a categorical variable was created to account for both pack–years and time since quitting tobacco smoking in males (see Table 1). For females, we adjusted for tobacco smoking using a continuous log-transformed pack–years variable, again due to the small numbers of exposed participants. We used a continuous variable to describe the intensity of alcohol in drinks of ethanol per day based on cumulative consumption (ml/day/15.6 ml of ethanol). Estimates from model 2 for respirable crystalline silica, chromium-VI, and chromium-VI & nickel were additionally adjusted for duration of exposure to asbestos, an established carcinogenic agent for laryngeal cancer in humans (3).

We calculated p-values for linear trend for duration and estimated cumulative exposure by applying a logistic regression model that included the variable of interest as continuous.

In addition to the main analyses, we applied exposure lags of 10 and 20 years in the years before diagnosis and interview to all agents and metrics. We conducted additional sensitivity analyses for the agents with largest numbers of exposed participants (asbestos and respirable crystalline silica). The potential effects of selection bias were investigated by limiting the sample to blue-collar workers only. We also examined the effects of excluding Latin America from the analyses (since SYN-JEM estimates were based on exposure data collected outside of this region).

RESULTS

We excluded participants with missing data on sex, age, occupational history, tobacco smoking, and alcohol use (213 cases and 471 controls). The resulting baseline analytic sample included 2256 laryngeal cancer cases (203 females; 2053 males) and 7857 control participants (1604 females; 6253 males).

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Table 1 shows study participant characteristics by disease status and sex. For both males and females the largest proportions of laryngeal cancer cases were in individuals aged 50-69 and in current smokers. For alcohol, the largest proportion of laryngeal cancer cases was in male (but not female) heavy drinkers.

Table 2 summarizes participants' 50th, 75th, and 90th percentile estimated cumulative exposure distributions by case/control status and sex. Exposures were lognormally distributed and typically higher for cases compared to control participants, except for exposure to asbestos among females. Other than chromium-VI and nickel, exposure correlations between agents were low ($r < 0.4$ for both duration and cumulative exposure). We observed weak correlations between cumulative exposure to all agents and tobacco smoking (log-transformed packyears) ($r < 0.10$), and between all agents and cumulative alcohol consumption ($r < 0.10$).

Tables 3-5 show odds ratios (ORs) for laryngeal cancer associated with the three exposure metrics assessed, for asbestos, respirable crystalline silica, chromium-VI & nickel, and chromium-VI, by two levels of adjustment for potential confounding. The addition of asbestos as a potential confounder in the models for respirable crystalline silica, chromium-VI & nickel, and chromium-VI produced only very small changes in effect estimates. For all agents, ORs were higher for ever exposed versus non-exposed in both males and females. For other analyses, the strongest associations were observed in males for asbestos at >90%ile cumulative exposure (OR=1.3, CI=1.0-1.6), respirable crystalline silica at 30+ years duration (OR=1.4, CI=1.2-1.7) and 75%-90%ile cumulative exposure (OR=1.4, CI=1.1-1.8), chromium-VI at >75%ile cumulative exposure (OR=1.9, CI=1.2-3.0), and chromium-VI & nickel at 20-29 years duration (OR=1.5, CI=1.1-2.2). Study-specific results for ever versus never exposed males across all four agent categories (eFigures 1-4; http://links.lww.com/EDE/B599) indicate some heterogeneity between studies; the direction and strength of individual study effects on pooled results varied between agents.

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Asbestos

Ever occupational exposure to asbestos occurred for 55% of male cases (55% of controls), and 12% of female cases (9% of controls) (Tables 3 and 4). In fully adjusted results for males, the greatest increases were observed in the highest categories of exposure duration (p-value for linear trend = 0.06) and estimated cumulative exposure (p-value for linear trend = 0.04). In fully adjusted results for females, ORs were increased for both the low exposure duration (50^{th} %ile cut-off of 5 years) and the low cumulative exposure ($<50^{th}$ %ile, or <0.35 f/ml–years) categories.

Respirable crystalline silica

Ever occupational exposure to respirable crystalline silica occurred for 41% of male cases (29% of controls), and for 19% of female cases (13% of controls) (Tables 3 and 4). In fully adjusted results for males, the greatest increases were observed for the highest category of exposure duration (p-value for linear trend <0.0001) and the $75\text{-}90^{th}$ %ile (or 1.95-3.55 mg/m^3–years) category of cumulative exposure (p-value for linear trend = 0.0002). In fully adjusted results for females, the strongest increases in ORs were observed in the highest categories of exposure duration ($\geq 50^{th}$ %ile, or ≥13 years) and cumulative exposure ($\geq 50^{th}$ %ile, or ≥0.93 mg/m^3–years).

Chromium-VI and nickel combined

Exposure to both chromium-VI and nickel in the workplace occurred in participants' work history for 24% of male cases (17% of controls) (Table 5). In fully adjusted results, the greatest increases in ORs were observed for the 20-29 years duration category (p-value for linear trend = 0.02) and for the highest categories of cumulative exposure (p-value for linear trend = 0.02). The interpretation of results obtained after standardizing and summing quantitative exposure estimates for chromium-VI and nickel were unchanged compared to when each metal was assessed independently in additional analyses, reflecting the high correlation of nickel with chromium-VI exposure.

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Chromium-VI

Ever exposure to chromium-VI without exposure to nickel occurred for 10% of male cases and 6% of male controls (Table 5). In fully adjusted results, the highest ORs were observed for the 20-29 years exposure duration category (p-value for linear trend = 0.04) and for the highest category of cumulative exposure (p-value for linear trend = 0.0014).

Additional analyses (males only)

Results did not differ substantially by exposure lag-times of 10 and 20 years (eTables 2-5; http://links.lww.com/EDE/B599). Analyses restricted to include only participants who had ever worked in a "blue-collar" job weakened effect estimates for asbestos and respirable crystalline silica (eTable 6; http://links.lww.com/EDE/B599). The exclusion of study participants from the Latin America study increased the strength of effect estimates in analyses of asbestos and respirable crystalline silica, but did not change overall interpretations (eTable 7; http://links.lww.com/EDE/B599).

DISCUSSION

This study analyzed the risk of laryngeal cancer in relation to occupational exposure to four known lung carcinogens (asbestos, respirable crystalline silica, chromium-VI, and chromium-VI & nickel). This was done by combining two unique data sources: a new quantitative job exposure matrix designed for large community-based human health studies (SYN-JEM), and case–control data with complete occupational history and detailed information on tobacco smoking and alcohol consumption from five studies within the International Head and Neck Cancer Epidemiology (INHANCE) Consortium. We observed increased risks of laryngeal cancer associated with all agents evaluated. In males, positive tests for linear trend ($p < 0.05$) (including unexposed participants) were observed for estimated cumulative exposure to all agents, and for duration of exposure to respirable crystalline silica, chromium-VI & nickel combined, and chromium-VI. The relationships in males were based on a larger number of exposed cases and controls, and results were more robust;

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interpretation of results in females was limited by the small number of exposed participants (see Table 5). For this reason, the following discussion will focus on comparisons of findings in males.

Asbestos

Findings from this study are in line with those of other studies of asbestos and laryngeal cancer (3,27). A recently conducted meta-analysis of 21 publications noted elevated risks of laryngeal cancer mortality with long study follow up (>25 years) (standardized mortality ratio [SMR] 1.70, 95% CI 1.43-2.02) and in high-exposure cohorts (SMR 2.07, CI 1.54-2.76) (27). A cohort study of asbestos miners in Northern Italy observed an increased SMR for laryngeal cancer (SMR 2.67, 95% CI 1.15-5.25) (28). It is notable that increased ORs were observed in the current community-based analyses despite the relatively low estimated cumulative exposure levels (less than 5 f/ml–years at the 90th %ile) compared to those reported in this and other industry-based cohorts (3).

Respirable crystalline silica

Few other studies on laryngeal cancer have examined exposure to silica dust quantitatively. In a case–control study in Turkey, ever exposure to silica dust showed an increased OR for laryngeal cancer (OR 1.5, CI 1.2-1.9) (29). In the same study, an exposure–effect relationship was observed with increasing intensity of silica exposure. However, an Uruguay-based study did not observe increased ORs for laryngeal cancer with ever exposure to silica dust (OR 0.9, CI 0.6-1.5), nor with increasing duration of exposure (1-20 years OR 1.1, CI 0.6-1.9; 21+ years OR 0.8, CI 0.5-1.5) (30). A meta-analysis of silica dust and laryngeal cancer observed an increased pooled odds ratio (OR 1.39, CI 1.17-1.67) of laryngeal cancer in workers exposed to silica dust in six case–control studies (includes some assessed in the current pooled analyses) that adjusted for smoking and alcohol consumption (31). In their review of 16 cohort studies, the same authors observed only small increases in SMRs and standardized incidence ratios related to silica dust exposure and silicosis; a clear interpretation of results was limited by lack of adjustment for smoking or alcohol consumption (31).

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Chromium-VI & Nickel and Chromium-VI

While ORs were increased in the highest categories of cumulative exposure for both the chromium-VI & nickel and chromium-VI groups, stronger effects were noted in those only exposed to chromium-VI. A possible explanation for this difference could relate to the distinct nature of these exposures across the two groups. For individuals co-exposed to nickel and chromium-VI, approximately 75% held metal working jobs (e.g., welder, metal worker) where exposure to finer metal fumes could be expected. For those exposed to chromium-VI but not nickel (e.g., masons, tile-setters, tanners, painters, etc.), with exposure to coarser aerosols expected, more deposition of chromium-VI in the upper respiratory tract, including the larynx, may have occurred. It is also possible that these individuals encountered other unmeasured co-exposures.

Several independent studies have identified occupational exposure to metal dust as a risk factor for laryngeal cancer (32–34), although studies assessing quantitative exposure–effect relationships between exposure to nickel and chromium-VI and laryngeal cancer could not be located.

Strengths and limitations

This study's quantitative exposure estimates were based on a large number of workplace measurements, where modeling incorporated determinants of exposure such as year and region (7,17). This level of detail is relatively unique in case–control studies of long-latency diseases. Results obtained from analyses of broad metrics (such as industry or occupation) can be useful for a number of purposes, such as to inform general intervention, compensation, and research activities; however, they cannot identify specific agents as risk factors for cancer (35). In contrast, the current study investigated laryngeal cancer risks associated with quantitative estimates of exposure to individual agents using full occupational histories, providing a stronger basis to support quantitative risk assessment and specific exposure reduction activities.

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The ability to identify one particular agent as a risk factor for cancer may be impacted by the potential for co-exposure to other carcinogenic agents. This study's large sample size permitted separate analyses of participants exposed to chromium-VI but not nickel, compared to those co-exposed to chromium-VI and nickel. The standardization and addition of chromium-VI & nickel exposures in their combined analyses was preferable to assuming equal effects through simple addition, although it did not entirely avoid this assumption.

Final models for respirable crystalline silica and metal agents adjusted for exposure to asbestos, an established laryngeal carcinogen. The only other established occupational risk factor for laryngeal cancer, strong inorganic acid mists, was not assessed in this study, although limited co-exposure would be expected given the main industries where acid mists occur (e.g., manufacturers of phosphate fertilizer, isopropyl and ethyl alcohols, sulfuric and nitric acids, and lead batteries (4)). Nevertheless, co-exposure to other carcinogenic substances in participants' work histories cannot be ruled out.

An inherent limitation of job exposure matrices is the potential for exposure misclassification, since all individuals in a given job category are assigned the same level of exposure. However, the strategy of applying the mean of all exposure measurements within an occupational group offers the benefit of a Berkson error structure, in which exposure–effect relationships are not attenuated but come with a loss of precision (36). Further, the quantitative job exposure matrix (SYN-JEM) used to develop the estimates in our study was based on a database of thousands of personal workplace measurements from 19 countries (17). Most of these measurements (77%) were collected in a representative manner (i.e., where the aim of sampling is to obtain exposure measurements representative of all workers with a given job title), although they were not obtained from the studies included in the current pooled analyses. While these personal measurements cover a wide period, from the 1970s to 2009, the majority were collected after 1975 (17). Since the job history period for INHANCE participants spanned 1915 to 2008, some of the modelled estimates for jobs held prior to

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1975 may not accurately reflect "true" exposures in earlier time periods. To address potential issues with back extrapolation for all SYN-JEM estimates, a constant maximum exposure level was assigned to jobs held earlier in the 20th century, to avoid the assignment of unrealistic levels (7). Some heterogeneity was noted between the individual studies used in these analyses, with variable direction and strength of effects noted across agents. We adjusted for study in the models in an attempt to address differences in time periods, geographic locations, and methodologies across individual studies.

Because the SYN-JEM did not include exposure data from Latin America, exposures for these participants were applied using regional estimates for Spain and Italy, based on expected similarities in working and seasonal conditions between the regions. While this likely introduced some degree of exposure misclassification, excluding Latin American study participants from the analyses of asbestos and respirable crystalline silica did not change overall interpretations of the effect estimates.

In addition to its relatively large sample size that increased precision, the INHANCE consortium case–control study data provided the benefit of detailed information on tobacco smoking and alcohol drinking, which is important to address the strong potential for confounding by these factors in analyses of laryngeal cancer. Adjustment for these variables substantially influenced effect estimates for asbestos (demonstrated by differences observed between Model 1 and Model 2 adjustments) while a lesser change was observed for respirable crystalline silica and metals. Nevertheless, residual confounding by misclassification of tobacco smoking and alcohol drinking might have affected the observed associations.

We cannot rule out selection bias in this study. While all studies frequency matched controls to cases based on age, sex (where relevant), and regional factors, participation rates for control participants (range of 62%-86%) were generally lower than those of cases (range of 82%-96%). We examined selection bias by restricting analyses to ever blue-collar workers; effects generally weakened but did not differ substantially from main results (eTable 6; http://links.lww.com/EDE/B599).

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Case–control studies are also generally susceptible to recall bias, which may lead to differential exposure misclassification. However, prior studies have not found evidence of recall bias when investigating differences in job history reporting validity between cases and controls (37,38). Further, validation studies that have assessed self-reported occupational histories against objective measures (e.g. company, pension, and union records) have reported generally consistent levels of agreement, i.e., between 70-90% (6)).

Conclusions

The results of this study support hypotheses of a carcinogenic effect of four lung carcinogens (asbestos, respirable crystalline silica, chromium-IV, and chromium-VI with nickel) on laryngeal cancer.

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Table 1: Descriptive characteristics of study participants (2256 laryngeal cancer cases and 7857 control participants), by sex

		MALES				FEMALES			
		Cases n = 2053		Controls n = 6253		Cases n = 203		Controls n = 1604	
Characteristic	Category	n	%	n	%	n	%	n	%
Age (years)	< 50	273	13	1237	20	27	13	330	21
	50-59	700	34	1926	31	68	34	399	25
	60-69	713	35	1989	32	61	30	478	30
	≥ 70	367	18	1101	18	47	23	397	25
Tobacco smoking (pack–years and years since quitting)	Never smoker	76	4	1789	29	28	14	971	61
	< 20 Pack–yrs and 10+ yrs since quit	125	6	1515	24	9	4	199	12
	< 20 Pack–yrs and 1-9 yrs since quit	64	3	222	4	2	1	51	3
	< 20 Pack–yrs and Current smoker	152	7	514	8	31	15	164	10
	21-40 Pack–yrs and 10+ yrs since quit	117	6	492	8	4	2	22	1
	21-40 Pack–yrs and 1-9 yrs since quit	118	6	240	4	8	4	25	2
	21-40 Pack–yrs and Current smoker	427	21	611	10	62	31	108	7
	> 40 Pack–yrs and 10+ yrs since quit	97	5	212	3	1	1	9	1
	> 40 Pack–yrs and 1-9 yrs since quit	161	8	193	3	6	3	18	1
	> 40 Pack–yrs and Current smoker	716	35	465	7	52	26	37	2
Alcohol drinking	Never drinker	110	5	484	8	70	35	502	31
	0 < drinks/day < 1	324	16	2201	35	74	37	848	53
	1 ≤ drinks/day < 3	481	23	2013	32	38	19	216	14
	3 ≤ drinks/day < 5	353	17	792	13	11	5	21	1
	≥ 5 drinks/day	785	38	763	12	10	5	17	1
Study	France multi-centre (1989-1991)	292	14	272	4	N/A	N/A	N/A	N/A
	France multi-centre (2001-2007)	444	22	2744	44	49	24	744	46
	Germany Heidelberg	207	10	693	11	17	8	65	4
	Latin America	643	31	1119	18	79	39	272	17
	Western Europe	467	23	1425	23	58	29	523	33

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Table 2: Estimated cumulative exposure distributions of exposed study participants by agent, sex, and case or control status

	Asbestos (Males)		RCS (Males)		Cr-VI–nickel (Males)		Cr-VI (Males)		Asbestos (Females)		RCS (Females)	
	Cases n = 1126	Controls n = 3426	Cases n = 833	Controls n = 1813	Cases n = 446	Controls n = 1035	Cases n = 155	Controls n = 285	Cases n = 24	Controls n = 147	Cases n = 38	Controls n = 38
CUMULATIVE EXPOSURE [a]												
median	0.98	0.56	1.2	0.88	2.1	2.1	0.011	0.008	0.28	0.35	1.0	0.93
75%ile	2.3	1.6	2.4	2.0	5.3	5.0	0.020	0.017	-	-	-	-
90%ile	4.3	3.2	4.0	3.6	-	-	-	-	-	-	-	-

RCS = Respirable crystalline silica; Cr-VI = Chromium-VI

[a] Cumulative exposure metrics used in all models (Tables 3-5) are based on distributions in exposed control participants; expressed in fibers (f)/ml–years for asbestos; mg/m^3–years for RCS and Cr-VI; unit–years for Cr-VI–nickel

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Table 3. Laryngeal cancer odds ratios (ORs) and 95% confidence intervals in relation to indices of occupational exposure to asbestos and respirable crystalline silica, Males

		ASBESTOS				RESPIRABLE CRYSTALLINE SILICA			
Exposure Indicator	**Category**	**Cases (%)**	**Controls (%)**	**Model 1[a]**	**Model 2[b]**	**Cases (%)**	**Controls (%)**	**Model 1[a]**	**Model 2[c]**
Ever exposure	Never	927 (45)	2827 (45)	1.0 (ref)	1.0 (ref)	1220 (59)	4440 (71)	1.0 (ref)	1.0 (ref)
	Ever	1126 (55)	3426 (55)	1.3 (1.2-1.4)	1.1 (0.99-1.3)	833 (41)	1813 (29)	1.3 (1.2-1.5)	1.3 (1.1-1.5)
Duration of exposure (years)	None	927 (45)	2827 (45)	1.0 (ref)	1.0 (ref)	1220 (59)	4440 (71)	1.0 (ref)	1.0 (ref)
	<10	488 (24)	1885 (30)	1.2 (1.0-1.3)	1.1 (0.92-1.2)	269 (13)	657 (11)	1.3 (1.1-1.6)	1.2 (1.0-1.4)
	10-19	204 (10)	526 (8)	1.4 (1.2-1.7)	1.2 (0.94-1.4)	171 (8)	393 (6)	1.2 (1.0-1.5)	1.2 (0.98-1.5)
	20-29	148 (7)	389 (6)	1.3 (1.1-1.6)	1.1 (0.84-1.3)	122 (6)	239 (4)	1.4 (1.1-1.8)	1.3 (1.0-1.7)
	30+	286 (14)	626 (10)	1.5 (1.2-1.7)	1.2 (1.0-1.4)	271 (13)	524 (8)	1.3 (1.1-1.6)	1.4 (1.2-1.7)
P test for trend					0.06				<0.0001
Excluding unexposed					0.39				0.13
Cumulative exposure[d]	None	927 (45)	2827 (45)	1.0 (ref)	1.0 (ref)	1220 (59)	4440 (71)	1.0 (ref)	1.0 (ref)
	<50 %ile	404 (20)	1710 (27)	1.1 (0.98-1.3)	1.1 (0.91-1.3)	321 (16)	904 (15)	1.2 (1.1-1.4)	1.2 (1.0-1.4)
	50-75 %ile	310 (15)	857 (14)	1.3 (1.1-1.6)	1.1 (0.93-1.3)	229 (11)	456 (7)	1.3 (1.1-1.6)	1.3 (1.1-1.6)
	75-90 %ile	222 (11)	515 (8)	1.3 (1.1-1.6)	1.1 (0.88-1.3)	181 (9)	272 (4)	1.6 (1.3-1.9)	1.4 (1.1-1.8)
	>90 %ile	190 (9)	344 (6)	1.7 (1.4-2.1)	1.3 (1.0-1.6)	102 (5)	181 (3)	1.4 (1.1-1.8)	1.3 (0.96-1.8)

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P test for trend	0.04	0.0002
Excluding unexposed	0.41	0.38

[a] Adjusted for study, age

[b] Adjusted for study, age, alcohol intake, tobacco smoking (pack–years and years since quitting)

[c] Adjusted for study, age, alcohol intake, tobacco smoking (pack–years and years since quitting), and exposure to asbestos

[d] Based on exposure distribution in male control participants (expressed in fibers (f)/ml–years for asbestos and mg/m^3–years for RCS; see Table 2)

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Table 4. Laryngeal cancer odds ratios and 95% confidence intervals in relation to indices of occupational exposure to asbestos and respirable crystalline silica, Females

		ASBESTOS				RESPIRABLE CRYSTALLINE SILICA			
Exposure Indicator	**Category**	**Cases (%)**	**Controls (%)**	**Model 1[a]**	**Model 2[b]**	**Cases (%)**	**Controls (%)**	**Model 1[a]**	**Model 2[c]**
Ever Exposure	Never	179 (88)	1457 (91)	1.0 (ref)	1.0 (ref)	165 (81)	1402 (87)	1.0 (ref)	1.0 (ref)
	Ever	24 (12)	147 (9)	1.5 (0.91-2.3)	1.1 (0.63-1.8)	38 (19)	202 (13)	1.1 (0.71-1.6)	1.3 (0.78-2.0)
Duration (years)[d]	None	179 (88)	1457 (91)	1.0 (ref)	1.0 (ref)	165 (81)	1402 (87)	1.0 (ref)	1.0 (ref)
	< 50 %ile	13 (6)	62 (3.9)	1.9 (1.0-3.7)	1.3 (0.66-2.6)	21 (10)	99 (6)	1.3 (0.77-2.2)	1.2 (0.65-2.1)
	≥ 50 %ile	11 (5)	85 (5)	1.1 (0.6-2.2)	0.85 (0.41-1.8)	17 (8)	103 (6)	0.87 (0.49-1.5)	1.3 (0.69-2.6)
Cumulative exposure[e]	None	179 (88)	1457 (91)	1.0 (ref)	1.0 (ref)	165 (81)	1402 (87)	1.0 (ref)	1.0 (ref)
	< 50 %ile	14 (7)	74 (5)	1.9 (1.0-3.4)	1.3 (0.66-2.5)	17 (8)	101 (6)	1.1 (0.60-1.9)	1.0 (0.53-1.9)
	≥ 50 %ile	10 (5)	73 (5)	1.1 (0.6-2.2)	0.83 (0.38-1.8)	21 (10)	101 (6)	1.1 (0.64-1.8)	1.5 (0.82-2.8)

[a] Adjusted for study, age

[b] Adjusted for study, age, alcohol intake, tobacco smoking (pack–years)

[c] Adjusted for study, age, alcohol intake, tobacco smoking (pack–years), and exposure to asbestos

[d] 50%ile cutoff: Asbestos: 5 years; Respirable crystalline silica (RCS): 13 years

[e] Based on exposure distribution in female control participants (expressed in fibers (f)/ml–years for asbestos and mg/m^3–years for RCS; see Table 2)

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Table 5. Laryngeal cancer odds ratios and 95% confidence intervals in relation to indices of occupational exposure to Chromium-VI / Nickel and Chromium-VI, **Males**

		CHROMIUM-VI–NICKEL				CHROMIUM-VI			
Exposure Indicator	**Category**	**Cases (%)**	**Controls (%)**	**Model 1[a]**	**Model 2[b]**	**Cases (%)**	**Controls (%)**	**OR Model 1[a]**	**OR Model 2[b]**
Ever exposure	Never	1453 (77)	4933 (83)	1.0 (ref)	1.00 (ref)	1453 (90)	4933 (95)	1.0 (ref)	1.0 (ref)
	Ever	445 (24)	1035 (17)	1.3 (1.1-1.5)	1.2 (1.0-1.4)	155 (10)	285 (6)	1.5 (1.3-1.9)	1.4 (1.1-1.8)
Duration of exposure (years)	None	1453 (77)	4933 (83)	1.0 (ref)	1.00 (ref)	1453 (90)	4933 (95)	1.0 (ref)	1.0 (ref)
	<10	209 (11)	520 (9)	1.1 (0.94-1.4)	1.0 (0.82-1.2)	58 (4)	115 (2)	1.6 (1.1-2.2)	1.5 (1.0-2.2)
	10-19	86 (5)	198 (3)	1.3 (1.0-1.8)	1.3 (1.0-1.8)	37 (2)	63 (1)	1.6 (1.0-2.4)	1.3 (0.78-2.0)
	20-29	61 (3)	129 (2)	1.5 (1.1-2.1)	1.5 (1.1-2.2)	25 (2)	37 (1)	1.9 (1.1-3.2)	1.7 (0.95-3.1)
	30+	89 (5)	188 (3)	1.5 (1.1-1.9)	1.2 (0.89-1.6)	35 (2)	70 (1)	1.3 (0.85-2.0)	1.2 (0.71-1.9)
P test for trend					0.02				0.04
Excluding unexposed					0.03				0.57
Cumulative exposure[c]	None	1453 (77)	4933 (83)	1.0 (ref)	1.0 (ref)	1453 (90)	4933 (95)	1.0 (ref)	1.0 (ref)
	<50 %ile	221 (12)	517 (9)	1.2 (0.96-1.4)	1.1 (0.87-1.3)	65 (4)	143 (3)	1.3 (0.93-1.7)	1.2 (0.82-1.6)
	50-75 %ile	111 (6)	260 (4)	1.4 (1.1-1.8)	1.3 (0.98-1.7)	37 (2)	72 (1)	1.3 (0.87-2.0)	1.4 (0.87-2.2)

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	>75 %ile	114 (6)	258 (4)	1.5 (1.1-1.9)	1.3 (0.97-1.7)	53 (3)	70 (1)	2.4 (1.7-3.5)	1.9 (1.2-3.0)
P test for trend					0.02				0.0014
Excluding unexposed					0.15				0.15

[a] Adjusted for study, age

[b] Adjusted for study, age, alcohol intake, tobacco smoking (pack–years and years since quitting), asbestos exposure

[c] Based on exposure distribution in male control participants (expressed in mg/m^3–years for Cr-VI and unit–years for Cr-VI–nickel; see Table 2)

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