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Original Contribution

Occupational Exposure and Laryngeal and Hypopharyngeal Cancer Risk in Central and Eastern Europe

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A multicenter case-control study was conducted during 1999–2002 in four European countries (Poland, Romania, Russia, and Slovakia) to evaluate the role of occupational exposures in risk of laryngeal/hypopharyngeal cancer. Male cancer cases (34 hypopharyngeal, 316 laryngeal) with full data on occupational history and non-occupational factors were compared with 728 hospital controls for occupational exposure to 73 suspected carcinogens. Occupational history was evaluated by industrial hygienists blinded to case/control status. Elevated risks for ever exposure to coal dust were found for both hypopharyngeal (odds ratio (OR) = 4.19, 95% confidence interval (CI): 1.18, 14.89) and laryngeal (OR = 1.81, 95% CI: 0.94, 3.47) cancer, with clear dose-response patterns. Inclusion of a 20-year lag in the analysis strengthened these associations. Hypopharyngeal cancer risk was also significantly associated with exposure to mild steel dust (OR = 3.04, 95% CI: 1.39, 6.64) and iron compounds and fumes (OR = 2.74, 95% CI: 1.29, 5.84), without clear dose-response relations. Laryngeal cancer was significantly associated with exposure to hard-alloys dust (OR = 2.23, 95% CI: 1.08, 4.57) and chlorinated solvents (OR = 2.18, 95% CI: 1.03, 4.61), without dose-response relations. A possible link between high formaldehyde exposure and laryngeal cancer was suggested. No association was found for exposure to asbestos or inorganic acid mists. These data indicate that occupational exposure to coal dust may play a role in laryngeal and hypopharyngeal cancer. Other possible relations need further evaluation.

hypopharyngeal neoplasms; laryngeal neoplasms; occupational exposure

Abbreviations: CI, confidence interval; OR, odds ratio.

In European populations, cancers of the larynx and hypopharynx are largely due to tobacco smoking and alcohol consumption, with evidence of a synergistic combined effect (1–3). There is also consistent evidence that low consumption of fruits and vegetables is associated with high risk, after adjustment for alcohol and tobacco use (4).

Besides these main risk factors, however, occupational exposures and employment in several industries and occupations also seem to play an important role in these cancers. There is sufficient evidence for carcinogenicity in humans of strong inorganic acid mist, as judged by the International Agency for Research on Cancer, with the majority

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of evidence being based on findings for laryngeal cancer (5). Several studies have suggested an association between laryngeal cancer and occupational exposure to agents such as mustard gas (6–9), hair dye (10), nickel (9, 11), wood dust (12, 13), rubber products (14), diesel/gasoline fumes (13, 15), formaldehyde (16, 17), asbestos (17, 18), organic solvents (17), mineral oil (15), and coal dust (16), although the level of evidence is inconclusive.

Here we report results from a large multicenter case-control study carried out in four European countries to investigate the associations between occupational exposures and risk of laryngeal/hypopharyngeal cancer. Seventy-three specific occupational agents were chosen on the basis of either suggestions from previous studies or an established role in lung cancer (19).

MATERIALS AND METHODS

The multicenter case-control study was conducted during 1999–2002 at four study centers in Central and Eastern Europe: Budapest, Romania; Lodz, Poland; Moscow, Russia; and Banská Bystrica, Slovakia. All persons aged 15–79 years with incident cases of histologically or cytologically confirmed laryngeal or hypopharyngeal cancer were included. Laryngeal cancer included cancer in any of the topographic subcategories of code C32 of the *International Classification of Diseases for Oncology* (20)—glottis, supraglottis, subglottis, laryngeal cartilage, overlapping lesion of the larynx, and larynx, unspecified. Cancer of the hypopharynx included the *International Classification of Diseases for Oncology* codes C13 (hypopharynx) and C12 (pyriform sinus). At all study centers except Moscow, hospital controls were collected within the framework of a concurrent case-control study of occupational risk factors for lung cancer being conducted by the same study teams. All controls were recruited within 6 months of the recruitment period for the cases. Since the interview team at the Moscow center differed from that used in the lung cancer study, an additional control group was recruited. Hospital controls were selected from a prespecified list of diseases that excluded other cancers and diseases related to tobacco or alcohol. Controls were frequency-matched to cases by age (±3 years). The distribution of the control diseases was very broad, with no diagnostic category making up more than 10 percent of the overall group. Excluding specific subgroups of controls did not change the overall results, indicating no significant bias from any particular subgroup of controls.

Specially trained interviewers interviewed both cases and controls. They were not blind with regard to the disease status of the subjects. The interviews elicited detailed information on socioeconomic and demographic variables, general health characteristics, tobacco smoking, alcohol consumption, dietary habits (based on the frequency of past consumption of selected food items), oral hygiene, and employment history. In particular, cases and controls were asked to report in chronologic order all of the jobs they had held for more than 1 year. The occupational interview consisted of a general questionnaire for each job; for 16 prespecified jobs, a specific questionnaire was also used. The general questionnaire was designed to elicit complete occupational history and additional information relevant to exposure assessment, including job titles, tasks, industries, starting and stopping dates, full-time/part-time status, working environments, and specific exposures. The separate, more specific questionnaire was completed for employment in any of the following jobs or industries: miner/quarryman, woodworker, painter, welder, insulation worker, toolmaker or machinist, motor vehicle mechanic, meat worker or farmer, and the steel, coke manufacture, foundry, glass, tannery, chemical, and rubber industries.

The occupational exposure assessment was completed by local experts, including chemists, industrial hygienists, and physicians, who were blind to the disease status of the subjects. They had practical experience in industrial hygiene and took into account regional differences in use of materials, production processes, and prevention measures and changes in exposure patterns within and across jobs/industries over time for the different exposures. Standardization of exposure assessment was ensured through yearly workshops and coding exercises. All participating study centers applied the same occupational questionnaires and the same protocol for expert assessment. Coding was based on a full task description for each specific job but not on self-reported exposures. For evaluation of the reliability of exposure assessment, interrater agreement among expert assessors validating chemical exposure reports was determined. Detailed results of the interrater agreement study have been published elsewhere (21). For each job, the experts scored exposure to 73 agents and groups of agents according to three dimensions: intensity, frequency, and confidence. Categories of intensity were based on agent-specific cutpoints. Categories of frequency represented the percentage of working time exposed and were estimated as a proportion: 1–4.9 percent, 5–30 percent, and >30 percent. Confidence represented the degree of certainty of exposure and had three levels: possible but not probable, probable, and certain.

We limited our analysis to men because there were too few women with laryngeal and hypopharyngeal cancer to analyze occupational risk factors for women. Thirty-four male cases with hypopharyngeal cancer, 316 male cases with laryngeal cancer, and 728 male hospital controls who had full information on occupational history and exposure to nonoccupational factors were included in the study.

We applied unconditional logistic regression modeling to study the relation between occupational exposure to 73 agents and risk of laryngeal/hypopharyngeal cancer (22). Results were adjusted for the potentially confounding effect of age (≤44, 45–49, 50–54, 55–59, 60–64, 65–69, and ≥70 years), country (Poland, Romania, Russia, Slovakia), tobacco smoking (continuous variable in pack-years), and lifetime alcohol consumption (continuous variable in grams). Statistical analysis was performed using the SAS (SAS Institute, Inc., Cary, North Carolina) and Stata (Stata Corporation, Chicago, Illinois) software packages. SAS was used to form the database, and Stata was used for statistical analysis. Odds ratios and 95 percent confidence intervals were computed using subjects who had never been exposed to the substance under study as the reference category. We studied linear trends by fitting categorical variables as continuous variables in the model. We applied different approaches to calculate lifetime exposure to occupational agents, as follows.

1. ''Duration (years)''—duration of the exposed job period, in years.
2. ''Weighted duration (hours)''—total number of hours of effectively being exposed during a certain job period, based on total duration (in years) and frequency. As a measure of frequency, midinterval weighting for each interval was used (3 percent, 17.5 percent, and 65 percent).
3. ''Cumulative exposure (mg/m^3-hours)''—the product of the exposure intensity and the duration of the effectively exposed job period. As a measure of intensity, the midpoint of each agent-specific intensity category was used.

Separate analyses were conducted for cancers of the larynx and hypopharynx. Each analysis used the same control group. Analyses were repeated including a 20-year lag period that ignored exposures incurred 20 years prior to the date of interview. Additional analyses were performed taking into account levels of confidence. For categorical analyses of weighted duration and cumulative exposure, categories were based on the distribution among exposed controls, with tertiles used as cutoff points; subjects never exposed to the agent under study constituted the reference category.

RESULTS

A total of 34 hypopharyngeal cancer cases, 316 laryngeal cancer cases, and 728 controls were included in the study. Table 1 summarizes the characteristics of the study group by country, age, alcohol consumption, and smoking.

TABLE 1. Characteristics of cases and controls included in a study of laryngeal and hypopharyngeal cancer in Central and Eastern Europe, 1999–2002

	Cases				Controls	
	Hypopharyngeal cancer		Laryngeal cancer			
	No.	%	No.	%	No.	%
Country						
Romania	1	2.9	54	17.1	165	22.7
Poland	0		154	48.7	162	22.2
Russia	24	70.6	97	30.7	324	44.5
Slovakia	9	26.5	11	3.5	77	10.6
Age group (years)						
<44	1	2.9	20	6.3	63	8.65
45–49	4	11.8	36	11.4	94	12.9
50–54	4	11.8	56	17.7	114	15.7
55–59	10	29.4	56	17.7	113	15.5
60–64	5	14.7	46	14.6	123	16.9
65–69	5	14.7	51	16.1	113	15.5
≥70	5	14.7	51	16.1	108	14.8
Tobacco smoking						
Never smoker	1	2.9	9	2.8	179	24.5
Ex-smoker	6	17.7	61	19.3	218	30.0
Current smoker	27	79.4	246	77.7	331	45.5
Alcohol consumption						
Never drinker	0		3	1.0	20	2.7
Ever/current drinker	34	100	313	99.0	708	97.3
Total	34		316		728	

Table 2 shows the laryngeal cancer risk associated with ever exposure to 43 agents for which there were at least 10 exposed cases. Occupational exposure to hard-alloys dust (odds ratio (OR) = 2.23, 95 percent confidence interval (CI): 1.08, 4.57) and chlorinated solvents (OR = 2.18, 95 percent CI: 1.03, 4.61) showed statistically significant positive associations with laryngeal cancer. When analyses were restricted to exposures that were evaluated with a ''high'' level of confidence, the odds ratios for laryngeal cancer were 2.40 (95 percent CI: 1.03, 5.59; 11 cases) for hard-alloys dust and 1.62 (95 percent CI: 0.66, 3.99; nine cases) for chlorinated solvents. An increased risk of laryngeal cancer, though not significant, was found for exposures to approximately 20 substances. These agents were selected for further analyses in relation to duration of exposure, weighted duration, and cumulative exposure. Only coal-dust exposure showed a clear dose-response pattern with duration ($p = 0.01$), weighted duration ($p = 0.03$), and cumulative exposure ($p = 0.05$) (table 3). The inclusion of a 20-year lag period in the analysis strengthened these associations (test for trend: $p = 0.01$ for duration, $p = 0.007$ for weighted duration, and $p = 0.03$ for cumulative exposure). An increased risk of laryngeal cancer was observed for Poland (OR = 4.09, 95 percent CI: 1.59, 10.52) but not for other countries. Dose-response trends for duration ($p = 0.01$), weighted duration ($p = 0.03$), and cumulative exposure ($p = 0.05$) were also found in the Poland subgroup. The associations between occupational exposure to coal dust and smoking or alcohol remained in different groups of smokers or drinkers, with no evidence of any interaction, although odds ratios became generally nonsignificant. No significant associations were found for other substances studied.

Exposure to formaldehyde (OR = 1.68, 95 percent CI: 0.85, 3.31) was associated with a statistically nonsignificant increase in the risk of laryngeal cancer. The odds ratio increased with duration of exposure ($p = 0.06$) and cumulative exposure ($p = 0.07$). The odds ratio for the highest level of cumulative exposure to formaldehyde (≥22,700 mg/m^3-hours) was 3.12 (95 percent CI: 1.23, 7.91).

Neither exposure to hard-alloys dust nor exposure to chlorinated solvents showed a significant association with laryngeal cancer when data were analyzed according to different levels of duration, weighted duration, and cumulative exposure. Furthermore, there was no significant association between laryngeal cancer and any index of exposure to inorganic acid mists, even in the highest categories of duration

TABLE 2. Odds ratio for laryngeal cancer according to ever exposure to selected agents,* Central and Eastern Europe, 1999–2002

Exposure	No. of controls	No. of cases	Odds ratio†	95% confidence interval
Asbestos (general exposure)	65	26	0.86	0.51, 1.45
Chrysotile asbestos	54	21	0.78	0.44, 1.40
Sand	210	98	1.00	0.72, 1.38
Respirable free crystalline silica	22	10	1.10	0.46, 2.61
Soot	37	19	1.30	0.68, 2.48
Ashes	11	10	1.73	0.64, 4.71
Plastics pyrolysis products	62	28	1.01	0.60, 1.71
Formaldehyde	30	18	1.68	0.85, 3.31
Live animals	35	15	0.86	0.43, 1.74
Mineral spirits	75	39	0.81	0.51, 1.30
Dusts				
Inorganic insulation	44	15	0.86	0.44, 1.68
Abrasives	164	84	1.20	0.86, 1.69
Concrete	97	46	0.77	0.50, 1.18
Cement	102	40	0.71	0.46, 1.11
Brick	46	28	1.08	0.62, 1.80
Coal	24	26	1.81	0.94, 3.47
Wood (general)	74	24	0.81	0.48, 1.37
Hard wood	29	10	0.73	0.32, 1.66
Soft wood	69	25	0.87	0.51, 1.48
Inorganic pigments	81	26	0.99	0.59, 1.65
Chromate (Cr^{VI})	44	17	0.87	0.45, 1.68
Mild steel	165	87	1.30	0.93, 1.82
Stainless steel	54	58	1.04	0.61, 1.78
Hard alloys	30	16	2.23	1.08, 4.57
Chromium and compounds	45	14	0.71	0.36, 1.41
Fumes or mists				
Chromate (Cr^{VI})	47	20	1.06	0.58, 1.93
Chromium and compounds	52	23	1.04	0.59, 1.85
Nickel and compounds	38	12	0.85	0.42, 1.75
Iron compounds	180	59	0.77	0.54, 1.12
Coal combustion	24	19	1.44	0.72, 2.86
Coke combustion	12	10	1.72	0.63, 4.70
Arc welding	167	56	0.78	0.54, 1.14
Gas welding	103	42	0.89	0.58, 1.37
Lubricating oil	161	90	1.19	0.84, 1.69
Cutting fluids	82	44	1.42	0.92, 2.20
Other mineral oils	46	16	1.05	0.54, 2.03
Inorganic acid	82	37	0.94	0.60, 1.49
Fuels and emissions				
Petroleum/gasoline engine emissions	124	68	1.34	0.92, 1.95
Diesel/kerosene engine emissions	155	74	1.18	0.83, 1.69
Gasoline/petroleum	116	53	1.31	0.88, 1.95
Diesel fuel/kerosene	107	45	1.20	0.80, 1.82
Solvents				
Organic solvents	219	97	1.04	0.76, 1.44
Chlorinated solvents	30	15	2.18	1.03, 4.61

* Agents with at least 10 cases classified as ever having been exposed.

† Odd ratios were adjusted for age, country, tobacco smoking, and alcohol consumption.

TABLE 3. Odds ratio for laryngeal cancer according to indices of exposure to coal dust, Central and Eastern Europe, 1999–2002

Exposure index	No lag				20-year lag			
	No. of controls	No. of cases	OR*,†	95% CI*	No. of controls	No. of cases	OR†	95% CI
Never exposed	704	290	1.00	Reference	708	292	1.00	Reference
Duration (years)								
1–4	13	6	0.75	0.25, 2.22	12	7	1.09	0.38, 3.15
5–14	8	11	2.36	0.83, 6.77	5	9	3.25	0.92, 11.47
≥15	3	9	5.61	1.26, 25.02	3	8	4.75	1.01, 22.22
Linear trend				$p = 0.01$				$p = 0.01$
Weighted duration (hours)								
0–1,299	6	3	0.89	0.18, 4.39	8	5	1.14	0.31, 4.21
1,300–2,499	8	3	0.63	0.15, 2.71	7	4	0.94	0.26, 3.47
≥2,500	10	20	3.34	1.38, 8.10	5	15	6.53	1.95, 21.8
Linear trend				$p = 0.03$				$p = 0.007$
Cumulative exposure (mg/m^3-hours)								
0–5,999	7	6	1.15	0.34, 3.90	8	8	1.51	0.51, 4.53
6,000–27,699	9	12	2.06	0.78, 5.46	5	10	3.28	0.97, 11.14
≥27,700	8	8	2.28	0.69, 7.51	7	6	2.13	0.57, 7.95
Linear trend				$p = 0.05$				$p = 0.03$

* OR, odds ratio; CI, confidence interval.

† Odd ratios were adjusted for age, country, tobacco smoking, and alcohol consumption.

(OR = 1.48, 95 percent CI: 0.80, 2.76) and weighted duration (OR = 1.28, 95 percent CI: 0.63, 2.59).

Table 4 shows odds ratios for hypopharyngeal cancer according to exposure to six occupational agents for which there were at least 10 exposed cases. The odds ratio for hypopharyngeal cancer was significantly increased with exposure to mild steel dust (OR = 3.04, 95 percent CI: 1.39, 6.64) and iron compounds and fumes (OR = 2.74, 95 percent CI: 1.29, 5.84). A significant increase in the odds ratio for hypopharyngeal cancer was also observed for exposure to coal dust, although only four cases were exposed (OR = 4.19, 95 percent CI: 1.18, 14.89). Introduction of a 20-year lag period in the calculation strengthened the association with hypopharyngeal cancer (OR = 4.54, 95 percent CI: 1.25, 16.48).

TABLE 4. Odds ratio for hypopharyngeal cancer according to ever exposure to selected agents,* Central and Eastern Europe, 1999–2002

Exposure	No. of controls	No. of cases	Odds ratio†	95% confidence interval
Sand	210	12	1.15	0.52, 2.55
Mild steel dust	165	14	3.04	1.39, 6.64
Iron compounds and fumes	180	19	2.74	1.29, 5.84
Diesel/kerosene engine emissions	155	10	1.50	0.66, 3.42
Arc welding fumes	167	14	1.55	0.72, 3.34
Organic solvents	219	14	1.68	0.79, 3.58

* Agents with at least 10 cases classified as ever having been exposed.

† Odd ratios were adjusted for age, country, tobacco smoking, and alcohol consumption.

Table 5 shows dose-dependent risks of hypopharyngeal cancer for exposure to mild steel dust and iron compounds and fumes. Although statistically significant dose-response relations were observed for weighted duration of exposure and cumulative exposure to mild steel dust and for duration and weighted duration of exposure to iron compounds and fumes, no dose-response patterns were apparent.

DISCUSSION

Tobacco smoking and alcohol consumption are the major etiologic factors for laryngeal cancer (1, 2). As reported elsewhere (Hashibe et al., International Agency for Research on Cancer (Lyon, France), unpublished manuscript), tobacco use was a strong risk factor for laryngeal cancer in this population, with a 15-fold increase in risk of laryngeal cancer among current smokers and a fivefold increase among ex-smokers. For alcohol drinking, our risk estimates were moderate, with an approximately threefold increase in laryngeal cancer risk for the upper categories of cumulative consumption. An interaction that was more than

TABLE 5. Odds ratio for hypopharyngeal cancer according to indices of exposure to mild steel dust and iron compounds and fumes, Central and Eastern Europe, 1999–2002

Exposure	No lag				20-year lag			
	No. of controls	No. of cases	OR*,†	95% CI*	No. of controls	No. of cases	OR†	95% CI
Mild steel dust								
Never exposed	563	20	1.00	Reference	576	21	1.00	Reference
Duration (years)								
1–4	41	7	4.80	1.69, 13.64	47	7	4.45	1.58, 12.57
5–14	42	3	3.38	0.86, 13.25	54	3	3.08	0.80, 11.80
$\geq$15	82	4	1.70	0.50, 5.74	51	3	1.50	0.37, 6.06
Linear trend				$p = 0.08$				$p = 0.09$
Weighted duration (hours)								
0–2,499	54	6	3.38	1.17, 9.78	62	5	2.56	0.83, 7.88
2,500–10,499	56	1	0.73	0.09, 5.90	64	4	2.00	0.59, 6.80
$\geq$10,500	55	7	4.89	1.69, 14.13	26	4	7.30	1.86, 28.75
Linear trend				$p = 0.006$				$p = 0.004$
Cumulative exposure (mg/m^3-hours)								
0–5,999	55	4	2.31	0.69, 7.72	65	4	1.95	0.59, 6.49
6,000–27,699	55	6	3.59	1.25, 10.30	43	6	4.47	1.53, 13.07
$\geq$27,700	55	4	3.34	0.90, 12.45	44	3	2.69	0.61, 11.81
Linear trend				$p = 0.006$				$p = 0.008$
Iron compounds and fumes								
Never exposed	548	15	1.00	Reference	578	17	1.00	Reference
Duration (years)								
1–4	43	6	3.59	1.19, 10.78	41	6	3.19	1.10, 9.27
5–14	53	5	2.56	0.82, 8.01	61	6	2.29	0.82, 6.41
$\geq$15	84	8	2.46	0.95, 6.35	48	5	2.52	0.79, 8.04
Linear trend				$p = 0.03$				$p = 0.03$
Weighted duration (hours)								
0–1,499	58	8	3.64	1.33, 9.96	63	9	3.08	1.24, 7.66
1,500–7,599	60	6	2.43	0.85, 6.93	55	3	1.04	0.27, 3.97
$\geq$7,600	61	5	2.30	0.72, 7.32	31	5	6.22	1.79, 21.68
Linear trend				$p = 0.04$				$p = 0.01$
Cumulative exposure (mg/m^3-hours)								
0–3,899	58	6	3.23	1.12, 9.35	53	6	2.86	1.01, 8.07
3,900–31,499	61	11	4.59	1.82, 11.59	55	9	4.05	1.56, 10.50
$\geq$31,500	60	2	0.78	0.16, 3.75	41	2	0.90	0.18, 4.42
Linear trend				$p = 0.10$				$p = 0.08$

* OR, odds ratio; CI, confidence interval.

† Odd ratios were adjusted for age, country, tobacco smoking, and alcohol consumption.

multiplicative was observed between ever use of tobacco and ever use of alcohol.

Although the only established occupational carcinogen for laryngeal cancer is exposure to strong inorganic acid mists containing sulfuric acid (5, 23), other occupational exposures have been possibly linked to laryngeal cancer, including mustard gas (9), hair dye (10), nickel (9), wood dust (13), rubber products (14), diesel/gasoline fumes (13, 15), formaldehyde (17), asbestos (17, 18), organic solvents (17), mineral oil (15), and coal dust (16). We examined the risk of laryngeal and hypopharyngeal cancers associated with occupational exposures using structured questionnaires to obtain detailed information on occupational history and lifestyle factors (tobacco smoking and alcohol consumption) to avoid their confounding effects.

The strongest association with laryngeal cancer in our study concerns coal dust, although the association was statistically significant only after inclusion of a 20-year lag period. There was a clear dose-response relation for duration, weighted duration, and levels of cumulative exposure: Laryngeal cancer risk increased with increasing levels of exposure to coal dust. These associations were observed only for Poland, not other countries. Taking into account the identical exposure assessment procedures used at all participating centers, the high level of agreement between expert teams, and the small study size, the lack of association between laryngeal cancer and exposure to coal dust in populations from other countries might be explained by a low prevalence of exposure to coal dust in those areas. Despite there being only four hypopharyngeal cancer patients who were exposed to coal dust, the odds ratio was significantly increased (OR = 4.19, 95 percent CI: 1.18, 14.89). Available categorical analysis also showed an exposure-response relation for weighted duration ($p = 0.03$). These results support the findings of studies from China (24) and France (16) in which there was a significant association between exposure to coal dust and laryngeal (Chinese study) and hypopharyngeal (French study) cancer. Since coal dust typically contains substantial amounts of mineral matter, of which quartz is an important component, silica dust may play an important role. In the present study, no association with exposure to respirable free crystalline silica was found for laryngeal cancer or hypopharyngeal cancer. In addition, when adjustment for free crystalline silica was performed, odds ratios for cancers of the hypopharynx and larynx did not substantially change.

In the present study, we observed some associations that have not been reported previously. Exposure to mild steel dust was associated with a significant increase in risk of hypopharyngeal cancer, although the dose response was ambiguous. Exposure to mild steel dust mainly occurs in processing of objects made of this alloy, such as cutting, abrading, machining, polishing, etc. As a rule, these operations are carried out under dry conditions. Significant dose-response gradients were observed for exposure to total mild steel dust but not for specific chemical components of dust (for example, any metal) or other steel dust. Sokic et al. (25) previously reported an excess risk of laryngeal cancer in relation to exposure to metal dust, without detailed specification of occupations potentially exposed to metal dust (26). To our knowledge, no such information exists for hypopharyngeal cancer. A study conducted in six Southern European areas (27) did not demonstrate such an association, although there was a nonsignificantly elevated risk for milling-machine operators and other machine-tool operators.

In our study, hypopharyngeal cancer was associated with exposure to iron compounds and fumes, although there was no monotonic increase in the odds ratio with increasing duration or cumulative exposure. These fumes are generated during high-temperature processes involving iron or iron-containing alloys, in occupations such as welding and sheet-metal working and in highly exposed industries such as foundries and smelting. There were some earlier observations of increased risk of laryngeal cancer among welders (28–30) and metal workers (13, 14, 31).

We observed an excess risk of laryngeal cancer among subjects exposed to hard-alloys dust and chlorinated solvents. However, no dose-response patterns were seen for these substances. Exposure to metal dust was linked to laryngeal cancer in previous studies (25–27), and it is possible that hard alloys were a part of the metal dust. Since an association between exposure to chlorinated solvents and cancer of the larynx has never before been reported, further studies are needed to clarify the association.

There is limited evidence suggesting a possible relation between formaldehyde exposure and the development of laryngeal cancer (32). In our study, no overall association was found between formaldehyde and laryngeal cancer, although the odds ratio was increased among workers with more than 22,700 mg/m^3-hours of cumulative exposure. Two recent studies also suggested a possible association between exposure to formaldehyde and laryngeal cancer (16, 17).

Asbestos is a known lung carcinogen (33), and its role in the etiology of laryngeal and hypopharyngeal cancer has been investigated extensively (34). We did not observe an association between any form of asbestos and laryngeal/hypopharyngeal cancer. Similarly, occupational exposure to strong inorganic acid mists containing sulfuric acid has previously been classified as carcinogenic to humans (5). The exposure category "strong inorganic acid mists" includes the mists of mixed inorganic acids (mainly hydrochloric acid), as well as nitric, phosphoric, chromic, hydrofluoric, and sulfuric acids. In previous studies concerning associations between laryngeal cancer and exposure to sulfuric acid, significant positive results were observed only among highly exposed subjects (23, 35). In our study, no dose-response effect was found between laryngeal cancer risk and exposure to inorganic acid mists. This may be explained by a lack of power in our study to detect moderate effects. A significant increase in risk of hypopharyngeal cancer was observed with exposure durations of more than 15 years (four cases; OR = 3.72, 95 percent CI: 1.08, 12.81), although further analysis of weighted duration and cumulative exposure to inorganic acid mists did not support this finding. Unfortunately, only five patients with hypopharyngeal cancer were exposed to these agents, and a detailed analysis was not feasible.

As with most case-control studies, our study had several limitations. The possibility of interviewer bias cannot be excluded, since the interviewers knew whether a respondent was a case or a control. Such a bias should have had the strongest effect on "soft" variables, such as the exposure checklist. However, the independent teams of experts evaluating the specific exposures for each subject were blind to the subject's status. Thus, interviewer bias was probably not a major limitation in this study.

Expert assessment of occupational exposures based on detailed occupational histories is the most accurate method of classifying exposure in community based case-control studies (36), although some level of exposure misclassification is still to be expected. A previous interteam agreement study including all occupational teams indicated that the specificity of assessment of "ever" exposure was above 0.94 for all agents, whereas sensitivity ranged between 0.39 and 0.89. Thus, some level of attenuation of the odds ratios could be expected, in spite of the advantages of our method and its ability to reduce misclassification relative to other methods of exposure assessment (21).

In conclusion, our study has demonstrated an association between coal dust exposure and risk of cancer of the larynx and hypopharynx. Associations between exposure to mild steel dust and iron compounds and fumes and hypopharyngeal cancer, as well as between exposure to hard-alloys dust and chlorinated solvents and cancer of the larynx, need further evaluation. Finally, we did not detect any increase in risk with exposure to inorganic acid mists.

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