A Population-Based Case-Control Study of Occupational Exposure to Acids and the Risk of Lung Cancer:

Evidence for Specificity of Association

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Occupational exposure to strong inorganic acid mists containing sulfuric acid has been recognized as a carcinogen (Group 1) since 1992. An augmented, secondary data analysis of a population-based case-control study of lung cancer was conducted to assess lung cancer-specific risks using 772 lung cancer cases diagnosed between 1981 and 1985. Individually matched controls—on age, gender, and borough of residence—were identified. Lifetime exposure to 10 acidic agents, including strong inorganic acids and some gases, was assessed from complete lifetime occupational histories in terms of concentration, frequency, and reliability of the various exposure assessments. Smoking-adjusted odds ratios and 95% confidence intervals were determined for overall and histology-categorized lung cancers using conditional logistic regression. No excess risk for overall lung cancer was associated with any of the acids, and effect modification by gender could not be identified. The absence of an acid lung cancer effect reinforces more recent toxicological data that suggest specificity to the larynx. *Key words*: lung cancer; larynx; acids; case-control study; occupational exposures.

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INTRODUCTION

The role of strong inorganic acids, sulfuric acid in particular, in the development of laryngeal and other upper-respiratory tract cancers was reported in 1982.[1,2] Subsequent studies have suggested that similar biological mechanisms attributable to strong inorganic acids might also play a role in the development of cancers of the lower airways[3] and of the bladder.[4] Based on previous reports of excess risk of human cancers, mainly laryngeal, associated with occupational exposure to sulfuric acid, the International Agency for Research on Cancer (IARC) originally listed "occupational exposure to strong-inorganic-acid mists containing sulfuric acid" as carcinogenic to humans (Group 1),[5] and more recently found sufficient evidence for cancer of the larynx and limited evidence for lung cancer.[6]

Strong inorganic acids are believed to be involved in cancer induction as acidic pH levels cause genotoxic damage in cells and can affect the toxicity of a number of chemicals.[7] Although the chronic toxicity of sulfuric acid on respiratory tract epithelium has been observed in animal studies, no direct evidence of carcinogenicity within the lung has been observed through direct-exposure animal models.[8] Also, histological or proliferative changes within lung epithelial tissue—indicative of carcinogenic effects—have not been observed.[9] Finally, recent investigations in human populations have not observed excess lung cancer risk.[10–12]

To further investigate the role of acids in the development of respiratory tract cancers, we had access to an existing population-based case-control study of lung cancer risk conducted in Toronto, Canada, among males and females. From this data set, which contained

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work histories, we inferred a range of acid exposures. This permitted us to conduct an augmented secondary data analysis to examine the association between lung cancer risk and lifetime occupational exposure to acids.

The major objective of the present study was to examine the role of exposure to specific acids (hydrochloric acid [HCl], nitric acid [HNO_3], sulfuric acid [H_2SO_4], and other acids), as well as other compounds with acidifying potential (sulfur dioxide [SO_2] and oxides of nitrogen [NO_x]) in the development of lung cancer, controlling for tobacco use, age, gender, and borough of residence. Attempts to refine further potential relationships between exposure to acids and histological subtypes were also pursued. The analysis also examined effect modification by gender of the relationship between acid exposures and lung cancer.

MATERIALS AND METHODS

This study was an augmented secondary data analysis of a population-based case-control study conducted in Toronto, Canada, from 1981 to 1985, designed to compare risk factors for lung cancer between males and females.[13] The original dataset was augmented by adding detailed worklife acid-specific exposures based on the occupational histories collected in the original study.

Lung cancer was defined as all primary cancers of the trachea, bronchus, and lung. Cases were identified using pathology, thoracic surgery, and other medical records from the 20 hospitals and the two referral centers in the Metropolitan Toronto area. Diagnosis was histologically confirmed for 98% of the cases. Female cases were all between 25 and 75 years of age and were diagnosed between January 1981 and March 1985. For each female case identified, one male case—matched by age (±4 years) and time of diagnosis (±1 month)—was randomly selected from these same hospitals.

Each male–female pair of cases was matched for age (±4 years) and borough of residence with the male–female pair of controls. Residential matching was accomplished by randomly sampling from complete enumeration lists for the boroughs comprising the Municipality of Metropolitan Toronto.

In order to include all cases in the study, proxy interviews, primarily with spouses, were conducted from 1982 to 1985 for those cases that had died. Of all cases interviewed, 35% were home-based proxy interviews; all others were direct personal home-based interviews. Of all eligible cases and controls, interviews were obtained for 442 female cases, 403 male cases, 410 female controls, and 362 male controls. To provide insight into response rates, in gathering the primary dataset, a total of 896 female cases were identified as eligible, and interviews were obtained for 442 (49%) of these. The remainder could not be interviewed owing to physician refusal ($n = 56$ [6%]), refusal by subjects or next of kin ($n = 166$ [19%]), and inability to trace, too sick, or other reasons ($n = 232$ [26%]). Of the 654 eligible male cases, 403 (62%) were interviewed, 32 (5%) interviews were refused by the physician, 98 (15%) were refused by the subjects or next of kin, and 121 (18%) could not be traced, were too sick, or could not be interviewed for other reasons.

The mean interval, from date of diagnosis to date of interview, for the live cases was 6.89 months; for deceased cases (that is, proxy interviews) the mean interval was 11.54 months. The median intervals were almost one month less in each group with ranges respectively of [0.74, 25.49] months for live cases, and of [0.93, 34.51] months for deceased (proxy) cases. Of the 845 cases obtained, 772 were individually matched to controls; the matched sets were used in our analysis. Among those identified controls for which contact was made, 66% agreed to participate.[13] The distribution of cases and controls by gender and histological lung cancer type, smoking status, and age is shown in Table 1.

In the initial study, detailed lifetime work histories were recorded in the interviewer-administered questionnaires, which had originally been developed and subsequently refined for earlier studies.[14–16] For the purposes of the present analysis, a highly trained and experienced team of occupational hygienists and chemists, led by one of the authors (RL), determined likely lifetime exposure profiles to each of 10 different acid categories: hydrochloric acid, acetic acid, nitric acid, hydrofluoric acid, sulfuric acid, phosphoric acid, hydrocyanic acid, and other acids, as well as sulfur dioxide and oxides of nitrogen (mainly NO and NO_2), these last two categories being included because they have acidic potential in the presence of water. The number of people in the category of exposure to "other acids" was quite small, which indicated that an even smaller number of people was associated with any one of the subcategories such as to exclude it as a separate category of exposure. These 10 substances were selected in consultation with the expert team of industrial hygienists as those acidic substances whose workplace presence was most likely. Occupational exposures to other potentially confounding substances such as asbestos, silica, coke oven emissions, or radon were not considered in this data set. Any of these latter exposures would tend to have had a relatively low exposure prevalence. While selected exposure assignments were verified through visits to related industrial complexes, no external validation of the assignments made by this expert team was undertaken. Any standard toxicology text will describe those industries associated with specific acids.[17]

The approaches used to construct individual exposure histories have been detailed elsewhere.[18,19] In short, the method is based on deriving a three-point scale for concentration, frequency, and reliability, based on the chronological job history sheets and an

TABLE 1 Distribution of the Lung Cancer Cases and Matched Controls[a] by Gender, Category of Lung Cancer Histology,[a] Smoking Status, and Age Group,[b] Toronto, Canada, 1981–1985

	Male				Female			
	Cases (n = 362)		Controls (n = 362)		Cases (n = 410)		Controls (n = 410)	
Variable	n	%	n	%	n	%	n	%
Histology								
Squamous cell carcinoma	141	40.1	0	0	101	25.7	0	0
Adenocarcinoma	87	24.7	0	0	106	27.0	0	0
Small- and oat-cell carcinoma	77	21.9	0	0	96	24.4	0	0
Large- and giant-cell carcinoma	23	6.5	0	0	29	7.4	0	0
Smoking								
Never	12	3.3	84	23.2	50	12.2	214	52.2
Ex-smoker (quit > 5 yrs)	57	15.7	135	37.3	27	6.6	77	18.8
Current (or, quit ≤ 5 yrs)	293	80.9	143	39.5	333	81.2	119	29.0
Age								
< 55 yrs	82	22.7	87	24.0	91	22.2	97	23.7
55–64 yrs	136	37.6	126	34.8	166	40.5	156	38.0
65–74 yrs	128	35.4	131	36.2	134	32.7	134	32.7
75+ yrs	16	4.4	18	5.0	19	4.6	23	5.6

[a]112 cases (n = 34 male and n = 78 female) had non-categorized or other histological diagnoses.
[b]Cases were matched to controls on gender, age, and borough of residence. Ages of matched pairs sometimes spanned table category breakpoints.

extensive library of period-specific documentation of industrial processes. For each of the jobs recorded by the study participants, the hygienists assigned a level of concentration, frequency of exposure, and reliability of the assessment associated with each of the acids/gases for that job/industry/period (circa the period in which the job was held).

The three exposure categories for concentration were low, medium, and high. The categories for frequency were low (1 to 5% of time), medium (5 to 30% of time), and high (≥ 30% of time). Reliability categories were based on confidence in the estimate as "possible," "probable," or "certain." The *a priori* strategy that we had adopted assumed that the "possible" category was more likely to be exposed than not. Our approach erred on the side of establishing an exposure-free referent group. The entire lifetime history of job exposures was thus reduced to an "$n \times 3$" matrix, where n equaled the number of jobs in each participant's life. This multidimensional coding of acid/gas exposure was then simplified as follows for use in the analysis of association with lung cancer.

The first summary exposure measure was a dichotomous variable specifying "any" exposure during a person's occupational lifetime. That is, if at any time in his or her life a person had a recorded frequency or concentration at or above the lowest level, regardless of reliability, he or she was classified as having experienced an exposure.

Each of the categories of concentration, frequency, and reliability were labeled respectively as "1," "2," and "3." Then, an exposure index was calculated as the summation over all jobs of the square of the product of the concentration, frequency, and reliability, multiplied by the duration in months. This index was divided by the total duration of exposure to give an average exposure level, a method extensively used by one of the authors (JS). The median of the distribution of this average exposure measure for those "ever" exposed was utilized to categorize the exposed group into high and low exposures, providing a trichotomized exposure measure. In our analysis, we also incorporated duration (≤ 10 years vs. > 10 years) into the "low" and "high" exposure categories. Using this approach, the unexposed category was identical across all categories of exposure. The distribution of the cases and controls by gender and acid categories is presented in Table 2.

A progressively more complex analytical approach to assessing the relationship between lung cancer risk and the various acids (individually) in their classification schemes was followed. First, each set of exposure categorizations was subjected to an unadjusted analysis using conditional logistic regression in STATA 10 (Stata Corporation, College Station, TX). Second, we forced an interaction term for the exposure variable and the gender of the participant into the model. Third, an adjusted conditional logistic regression model for each set of exposure categorizations, including adjustment for smoking (ln(1 + pack – years/5)) was conducted. Finally, each of these steps was repeated for each of four different lung cancer histological subtypes. Smoking-adjusted odds ratios (ORs) and 95% confidence intervals (95%CIs) are presented.

TABLE 2 Distribution of the Lung Cancer Cases and Matched Controls[a] by Gender and Exposure Level, Toronto, Canada, 1981–1985

	Male				Female			
	Cases (*n* = 362)		Controls (*n* = 362)		Cases (*n* = 410)		Controls (*n* = 410)	
Acids and Exposure Status[b]	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Hydrochloric acid								
Unexposed	252	69.6	246	68.0	342	83.4	359	87.6
Low exposure, short duration	19	5.2	33	9.1	26	6.3	22	5.4
Low exposure, long duration	45	12.4	43	11.9	5	1.2	8	2.0
High exposure, short duration	20	5.5	14	3.9	24	5.9	16	3.9
High exposure, long duration	26	7.2	26	7.2	13	3.2	5	1.2
Acetic acid								
Unexposed	314	86.7	314	86.7	390	95.1	376	91.7
Low exposure, short duration	15	4.1	12	3.3	6	1.5	12	2.9
Low exposure, long duration	12	3.3	14	3.9	1	0.2	8	2.0
High exposure, short duration	14	3.9	14	3.9	9	2.2	9	2.2
High exposure, long duration	7	1.9	8	2.2	4	1.0	5	1.2
Nitric acid								
Unexposed	338	93.4	335	92.5	399	97.3	404	98.5
Low exposure, short duration	8	2.2	5	1.4	8	2.0	4	1.0
Low exposure, long duration	4	1.1	9	2.5	1	0.2	1	0.2
High exposure, short duration	11	3.0	7	1.9	2	0.5	1	0.2
High exposure, long duration	1	0.3	6	1.7	0	0	0	0
Hydrofluoric acid								
Unexposed	346	95.6	348	96.1	405	98.8	408	99.5
Low exposure, short duration	4	1.1	7	1.9	1	0.2	0	0
Low exposure, long duration	2	0.6	2	0.6	2	0.5	0	0
High exposure, short duration	7	1.9	3	0.8	1	0.2	2	0.5
High exposure, long duration	3	0.8	2	0.6	1	0.2	0	0
Sulfuric acid								
Unexposed	219	60.5	208	57.5	341	83.2	349	85.1
Low exposure, short duration	46	12.7	39	10.8	29	7.1	26	6.3
Low exposure, long duration	25	6.9	33	9.1	7	1.7	6	1.5
High exposure, short duration	35	9.7	46	12.7	26	6.3	22	5.4
High exposure, long duration	37	10.2	36	9.9	7	1.7	7	1.7
Phosphoric acid								
Unexposed	330	91.2	334	92.3	400	97.6	395	96.3
Low exposure, short duration	12	3.3	13	3.6	3	0.7	10	2.4
Low exposure, long duration	14	3.9	7	1.9	1	0.2	1	0.2
High exposure, short duration	3	0.8	4	1.1	5	1.2	3	0.7
High exposure, long duration	3	0.8	4	1.1	1	0.2	1	0.2
Hydrocyanic acid								
Unexposed	355	98.1	353	97.5	402	98.0	405	98.8
Low exposure, short duration	1	0.3	2	0.6	4	1.0	2	0.5
Low exposure, long duration	3	0.8	2	0.6	0	0	2	0.5
High exposure, short duration	2	0.6	3	0.8	3	0.7	0	0
High exposure, long duration	1	0.3	2	0.6	1	0.2	1	0.2
Other acid(s)								
Unexposed	344	95.0	334	92.3	389	94.9	390	95.1
Low exposure, short duration	5	1.4	9	2.5	6	1.5	8	2.0
Low exposure, long duration	7	1.9	6	1.7	1	0.2	2	0.5
High exposure, short duration	5	1.4	11	3.0	10	2.4	7	1.7
High exposure, long duration	1	0.3	2	0.6	4	1.0	3	0.7
Oxides of nitrogen								
Unexposed	142	39.2	154	42.5	372	90.7	385	93.9
Low exposure, short duration	90	24.9	79	21.8	19	4.6	11	2.7
Low exposure, long duration	30	8.3	32	8.8	3	0.7	6	1.5
High exposure, short duration	47	13.0	50	13.8	10	2.4	8	2.0
High exposure, long duration	53	14.6	47	13.0	6	1.5	0	0

(*continued on next page*)

TABLE 2 (continued)

Acids and Exposure Status[b]	Male				Female			
	Cases (n = 362)		Controls (n = 362)		Cases (n = 410)		Controls (n = 410)	
	n	%	n	%	n	%	n	%
Sulfur dioxide								
Unexposed	227	62.7	217	59.9	381	92.9	380	92.7
Low exposure, short duration	54	14.9	58	16.0	19	4.6	19	4.6
Low exposure, long duration	28	7.7	33	9.1	5	1.2	5	1.2
High exposure, short duration	31	8.6	28	7.7	3	0.7	6	1.5
High exposure, long duration	22	6.1	26	7.2	2	0.5	0	0

[a]There were 772 matched pairs (n = 362 male and n = 410 female).
[b]Low exposure: below median level of exposure among those ever exposed; high exposure: above median level of exposure among those ever exposed; short duration: ≤ 10 years; long duration: > 10 years.

RESULTS

The results of the conditional logistic regression analyses for each of the acids, in multiple categories, by overall lung cancer risks and adjusted for smoking, are in Table 3. No excess risks were detected between the various acid exposures and overall lung cancer, adjusted for smoking and pair-matched for gender, age, and borough of residence. As an aggregate exposure to any of the acids under study, no observed excess risk was observed (OR, 0.95; 95%CI, 0.70–1.29). There was no indication that the exposure–cancer associations were modified by gender. Consequently, males and females were combined in all subsequent analyses. When we subdivided the low exposure and high exposure groups into subsets based on less than or equal to 10 years or more than 10 years of exposure, none of the subcategories exhibited particularly elevated ORs (results not shown in Table 3), and there were no discernable exposure–response trends across levels of these subcategories.

In general, OR estimates were very unstable for several of the acids (acetic acid, nitric acid, hydrofluoric acid, phosphoric acid, hydrocyanic acid, and "other" acids) to which relatively few participants had any lifetime exposures. In contrast, adequate numbers of exposures to sulfur dioxide, oxides of nitrogen, sulfuric acid, and hydrochloric acid allowed calculation of stable estimates.

Study cases consisted predominantly of squamous-cell carcinoma (31%) followed by adenocarcinoma (25%) and small-cell and oat-cell cancers, with fewer large-cell and giant-cell carcinomas (7%). The remaining 13% of cases were of mixed/unclear histology or of rare subtypes, and 2% were not histologically verified. The effects of each acid are presented separately by histology in Table 4. A few histology-specific associations were found: one elevated OR for squamous-cell carcinoma associated with acetic acid exposure (OR, 4.07; 95%CI, 1.53–10.78); two inverse ORs, one for adenocarcinoma associated with sulfur dioxide (OR, 0.40; 95%CI: 0.21–0.76), and one for small cell carcinomas associated with hydrocyanic acid (OR, 0.04; 95%CI: 0.00–0.70). Effect modification by gender was not apparent according to histology in this study in those analyses where the number of women was large enough.

Further analyses were conducted among only those participants directly interviewed. No differences were observed. In addition, analyses were conducted separately for males and females. Again, no difference in any of the risk estimates was observed.

DISCUSSION

This augmented secondary data analysis of a population-based case-control study did not demonstrate excess risks for any of a variety of acidic agents including strong acids such as hydrochloric, nitric, sulfuric, and phosphoric acids on the development of overall lung cancer. This finding is consistent with animal-model investigations of respiratory-tract carcinogenicity.[9]

Although IARC listed occupational exposures to strong inorganic acid mists containing sulfuric acid as carcinogenic (Group 1), sufficient evidence had existed for only upper-respiratory tract cancers, particularly laryngeal cancer.[5] More recently, IARC reaffirmed the designation of strong inorganic acid mists as a carcinogen (Group 1) with sufficient evidence for laryngeal cancer, but with only limited evidence for lung cancer.[6]

This recent revision listed the evidence for lung cancer as limited[6] because recent investigations in human populations have not observed excess lung cancer risk.[11,12] Furthermore, research in animal models has not demonstrated these types of histological or proliferative effects within lung epithelial cells suggestive of carcinogenicity.[8] By a mechanism that is likely quite different from that operating in the airways, Soskolne et al[4] did demonstrate an association between sulfuric acid exposure and bladder cancer.

Because of matching on gender in the primary dataset, our study participants in the augmented data

TABLE 3 Odds Ratios for Lung Cancer for Each Acid Measured by Intensity and Duration,[a] Toronto, Canada, 1981–1985*

	Any Exposure			Low Exposure			High Exposure		
Acids	Exposed Cases/ Controls	OR	95%CI	Exposed Cases/ Controls	OR	95%CI	Exposed Cases/ Controls	OR	95%CI
Hydrochloric acid	178/167	0.98	0.71–1.35	95/106	0.80	0.53–1.22	83/61	1.24	0.79–1.96
Acetic acid	68/82	0.97	0.61–1.53	34/46	0.89	0.49–1.62	34/36	1.08	0.57–2.05
Nitric acid	35/33	1.19	0.58–2.45	21/19	1.04	0.42–2.56	14/14	1.41	0.47–4.20
Hydrofluoric acid	21/16	1.44	0.63–3.33	9/9	1.44	0.40–5.25	12/7	1.44	0.48–4.29
Sulfuric acid	212/215	0.90	0.66–1.24	107/104	0.96	0.64–1.44	105/111	0.88	0.58–1.32
Phosphoric acid	42/43	0.81	0.45–1.47	30/31	0.81	0.41–1.61	12/12	0.83	0.26–2.59
Hydrocyanic acid	15/14	0.78	0.29–2.01	8/8	0.66	0.19–2.33	7/6	1.02	0.20–5.05
Other acid(s)	39/48	0.74	0.42–1.33	19/25	0.71	0.32–1.59	20/23	0.78	0.33–1.82
Oxides of nitrogen	258/233	0.95	0.66–1.36	142/128	0.96	0.66–1.41	116/105	0.97	0.64–1.47
Sulfur dioxide	164/175	0.72	0.50–1.02	106/115	0.74	0.49–1.11	58/60	0.79	0.46–1.32

*All $p > 0.05$.
[a]Referent category is the unexposed group for all classification schemes. Cases were pair-matched on age, gender, and borough of residence ($n = 772$ pairs). Models were adjusted for smoking (ln(1+ pack – years/5)). Low exposure: below median level of exposure among those ever exposed. High exposure: above median level of exposure among those ever exposed.

set consisted of an almost equal number of males and females. Previous investigations into differential susceptibility by gender have suggested that females may have a higher susceptibility to lung cancer from tobacco exposure than males.[21] However, an examination of potential effect modification by gender in our augmented data set did not uncover any statistically significant interaction. It should be noted that sample sizes in gender-specific strata may not have had adequate power to detect the associations under investigation. The use of female cases to examine what is typically an occupational exposure may have led to lower frequencies of exposure as many of the exposures of interest were found predominantly in manufacturing and processing industries, historically populated by males. Furthermore, the method used for acid exposure characterization was developed for assessing exposure among men.[20] This may also have resulted not only in lower frequencies of exposures, but also in less precise estimations of exposure whereby women would be more often "possible" for exposure. Consequently, lower estimates of exposure for women would have been estimated.

For acetic acid, excess risk for squamous-cell carcinoma was detected. Previous investigations have focused more heavily on other acids. In the current study, no significant effects were observed with acetic acid, except for squamous cell carcinoma. A positive finding for acetic acid was found for another histological subtype, oat-cell carcinomas, by Siemiatycki.[20] No association was found between acetic acid and overall lung cancer by Baccarelli et al.[11] It is possible, however, that acetic acid may have shown a specific association with small-cell and oat-cell carcinomas owing to previous investigations not examining acid-specific effects on the various lung cancer histological subtypes. It should be noted that the small sample size associated with acetic acid exposure could render instabilities in our own estimates. Finally, unlike sulfuric acid, acetic acid is volatile, with human exposure more to vapors than to mists. Vapors are more likely to penetrate further into the respiratory tract than the large particles that exist in mists.

An inverse association for adenocarcinoma was seen with exposure to sulfur dioxide. Similarly, inverse associations were seen for small-cell and oat-cell carcinoma with exposure to hydrocyanic acid. For these observed associations, the numbers of individuals in each of the histological subtypes as well as the numbers of exposed study participants were low and confidence intervals were wide. As indicated previously, the issue of small sample size may have explained some or all of these associations; hence they must be interpreted with caution. Overall, the large number of comparisons could well account for some of the statistical (positive as well as negative) findings in this study.

Thus, despite evidence for an effect of strong-inorganic-acid mists, particularly sulfuric acid, on the development of upper-respiratory tract cancers,[22] there appears to be only limited evidence for a similar effect in the lower airways. This poses several interesting questions. First, is this merely a result of the chemical failing to reach the lower airways? Measurements of particle sizes in occupational sulfuric acid exposure in lead-acid battery plants have indicated average particle sizes of approximately 5 microns (μm).[23] Particle size is critical in considering where acid mists are deposited[24] and model-based estimates suggest that 90% of 5 μm particles will be deposited in the upper-respiratory tract and will not reach the alveoli.[5] Only a fraction of the mist to which the larynx is exposed will therefore reach the lungs to elicit potential effects.

Second, do the airflow patterns through the larynx lead to deposition and adsorption of acids onto the laryngeal epithelium? Conclusions from reports in

TABLE 4 Odds Ratios for Lung Cancer for Each Acid Separated by Histology,[a] Toronto, Canada, 1981–1985

	Any Exposure to Acids within Histology Groups											
	Squamous Cell Carcinoma			Adeno-carcinoma			Small-cell and Oat-cell Carcinoma			Large-cell and Giant-cell Carcinoma		
Acids	**Exposed[b]**	**OR**	**95% CI**	**Exposed[b]**	**OR**	**95% CI**	**Exposed[b]**	**OR**	**95% CI**	**Exposed[b]**	**OR**	**95% CI**
Hydrochloric acid	64/48	1.66	0.85–3.25	50/44	1.06	0.61–1.84	31/40	0.54	0.23–1.25	12/9	1.01	0.26–3.91
Acetic acid	36/21	4.07*	1.53–10.8	11/18	0.48	0.18–1.26	9/21	0.56	0.17–1.89	3/5	0.29	0.04–2.33
Nitric acid	15/11	2.23	0.68–7.39	9/6	1.70	0.41–7.04	5/11	0.33	0.05–2.10	2/2	0.36	0.02–5.54
Hydrofluoric acid	6/5	0.62	0.11–3.40	6/3	1.81	0.42–7.80	8/5	3.65	0.52–25.6	0/0	—	
Sulfuric acid	48/52	1.14	0.64–2.05	82/65	0.73	0.40–1.33	47/50	1.12	0.52–2.42	14/17	0.58	0.16–2.04
Phosphoric acid	11/8	0.80	0.20–3.19	14/11	0.92	0.35–2.39	12/9	1.98	0.50–7.89	8/2	0.60	0.10–3.56
Hydrocyanic acid	3/4	0.41	0.06–2.66	7/3	1.99	0.34–11.6	2/5	0.04*	0.00–0.70	2/0	—	
Other acid(s)	19/11	1.68	0.52–5.41	9/14	0.84	0.30–2.29	5/8	0.81	0.17–3.86	2/4	0.14	0.00–2.05
Oxides of nitrogen	95/84	0.99	0.48–2.04	65/63	0.66	0.35–1.23	58/46	1.92	0.77–4.80	17/14	1.84	0.50–6.77
Sulfur dioxide	66/61	0.70	0.35–1.40	29/49	0.40*	0.21–0.76	38/37	1.33	0.54–3.25	14/7	2.10	0.60–7.37

*$p < 0.05$

[a]Referent category is the unexposed group. Cases were matched to controls on age, gender, and borough of residence ($n = 242$ pairs of squamous cell carcinoma, 193 pairs of adenocarcinoma, 173 pairs of small-cell and oat-cell carcinoma, 52 pairs of large-cell and giant-cell carcinoma). Models were adjusted for smoking (ln(1+ pack – years/5)).

[b]Exposed cases/controls.

animal models have suggested that it is probable that the airflow patterns within the larynx create a higher likelihood of sulfuric acid aerosol deposition in the larynx than the lungs and nasal passages; no effects were observed within the nasal passages in rat models either, only within the larynx.[9] Airflow patterns within the larynx would, in combination with the particle sizes, allow for persistent contact, deposition, and adsorption of acid mists with the surface of laryngeal epithelium before effective carcinogenic doses would reach the bronchioles and/or alveoli. This airflow-anatomy feature provides a physiological basis for the consistent effects of elevated laryngeal cancer risk, not lung cancer, and the absence of an effect in our investigation, particularly for sulfuric acid. This absence of effect is even more likely to take place in a context of overall low prevalence and levels of exposure as was probable in the present population-based case-control study.

Third, if the acidic agents do reach the lower airways (which is more likely for the gaseous substances), do the mechanical and cellular mechanisms of injury and repair in these regions differ for the different agents? Conflicting results were observed for sulfur dioxide only among adenocarcinomas; however, multiple comparisons could account for this finding.

One potential further limitation to the conclusions of this analysis is noteworthy: The conditional logistic regression analyses were adjusted using the matched pairs based on age, gender, and borough of residence as well as for smoking using the term $ln(1 + \text{pack} - \text{years}/5)$. However, it is possible that other factors such as family history could have confounded the association.

In conclusion, the data set in the present analysis, augmented using a detailed review of job histories by trained chemists and hygienists, provided a basis for attributing occupational exposures to various acids. This efficient use of the data set enabled the inference of a fine resolution of agent-specific exposure classification for analysis. This analysis did not demonstrate excess risks for any of a variety of acids on the development of lung cancer.

These results, in conjunction with previous epidemiological literature and recent animal models, suggest an agent-specific relationship not between sulfuric acid and lung cancer, but rather with laryngeal cancer. This finding, reinforced from more recent toxicological data, lends support to the laryngeal specificity of carcinogenic effects from long-term workplace acid exposures.

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