ABSTRACT

This study investigated arsenic and lung cancer incidence in a community setting in the Montreal area. Job histories and sociodemographic factors were collected by interview from 857 lung cancer cases, 533 general population controls, and 1,360 controls with other cancers. Chemist-hygienists assessed each subject's lifetime occupational exposure to 294 substances. Logistic regressions yielded arsenic/lung cancer odds ratios of 1.1 (95% confidence interval = 0.60, 1.7) based on cancer controls, and 0.82 (95% confidence interval = 0.41, 1.6) based on population controls. Risk did not rise with increasing level or probability of exposure.

Worksite studies consistently show lung carcinogenicity from arsenic. Since confounding from other chemicals was well controlled, the most likely explanation is substantially lower exposures than in previous studies. The lack of association in this study demonstrates the need for caution in interpreting negative findings from population-based case-control studies, particularly when exposures are low or rare, as well as the difficulty in generating hypotheses from such studies.

ABRÉGÉ

Cette étude a évalué le rôle de l'arsenic sur l'incidence du cancer du poumon dans la population générale montréalaise. Au total, 857 cas de cancer du poumon, 533 témoins de la population générale et 1 360 témoins atteints d'autres cancers ont été interrogés afin d'obtenir leur histoire professionnelle et leurs caractéristiques socio-démographiques. Des chimistes-hygénistes ont évalué l'exposition à 294 substances au cours de leur vie professionnelle. Les régressions logistiques ont abouti à un rapport de cotes de 1,1 (intervalle de confiance à 95 % = 0,6-1,7) pour le cancer du poumon suite à l'exposition à l'arsenic en se basant sur les témoins avec cancer, et de 0,82 (intervalle de confiance à 95 % = 0,4-1,6) en se basant sur les témoins de la population. Le risque n'augmentait pas en fonction du niveau ou de la probabilité d'exposition.

Les études menées en milieu de travail indiquent de façon répétée que l'arsenic est un agent cancérigène pulmonaire. Puisqu'un bon ajustement était fait pour d'autres substances potentiellement confondantes, l'explication la plus plausible est que les expositions étaient plus faibles que dans les études précédentes. L'absence d'association dans cette étude démontre qu'il faut user de prudence en interprétant des résultats négatifs obtenus lors d'études cas-témoins menées dans la population, particulièrement lorsque les expositions sont faibles ou rares, et qu'il est difficile de générer des hypothèses à partir de telles études.

When to be Skeptical of Negative Studies: Pitfalls in Evaluating Occupational Risks Using Population-based Case-control Studies

Sub-Woan Hu, DDS, PhD,¹ Irva Hertz-Picciotto, PhD,¹ Jack Siemiatycki, PhD²

Previous studies have reported a strong, significantly positive association between arsenic exposure and the risk of lung cancer,¹⁻¹² with relative risks ranging from 2 to over 20. Most investigations were of refinery workers, but miners and pesticide manufacturing workers have also been studied. It is not clear whether such associations can be detected in population-based studies where a broader range of industrial situations involving low-level occupational arsenic exposure might occur. We analyzed data from the Montreal population-based case-control study,¹³ which utilized in-depth interviews and expert assessments regarding a large number of occupational exposures, to evaluate risk for lung cancer from arsenic exposure.

METHODS

This investigation used data from a large case-control study of risk factors for cancer in the workplace among males aged 35-70, resident in the area of Montreal.¹⁴⁻¹⁸ Histologically confirmed incident cases of 20 sites of cancer diagnosed 1979-85 were included. Informed consent and in-person interviews were conducted in hospital or at home with completed questionnaires obtained on 3,726, or 83% of cases. Of 1,082 eligible lung cancer subjects, 79% responded. A cancer control group was constituted of all other sites (n=1,360),

restricted to subjects ascertained in the three years during which lung cancer patients were being ascertained.

A second, population-based, control group was constructed from electoral lists and random digit dialing, age-stratified to match the distribution of cancer patients. Seventy-two percent of 740 eligible population controls participated. If a case or control could not be interviewed, a proxy was.

The questionnaire consisted of: (a) a structured section requesting information on potential confounders such as age, ethnic group, education, family income, alcohol consumption, cigarette smoking, etc., and (b) a semi-structured probing section designed to obtain a detailed description of each job the subject had in his working lifetime. Interviewers were trained to probe for information on the company's activities, raw materials, final product and machines used, the man's responsibilities for machine maintenance, type of room or building in which he worked, activities of workmates around him, presence of gases, fumes or dusts, and any other information pertinent to possible chemical or physical exposures incurred by the subject.

Exposure assessment

A team of chemists and hygienists examined each completed questionnaire and translated each job into a list of potential exposures using a checklist of 294 substances. For this retrospective exposure assessment, the chemists relied on their own industrial experience and chemical knowledge, old and new technical and bibliographic material describing industrial processes, consultations with experts familiar with particular industries, and previously coded files in the same job category. For

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each product thought to be present in each job, the chemists noted three dimensions, each on a 3-point scale: their degree of confidence that the exposure had actually occurred (possible, probable, definite), the frequency of exposure during a normal working week (1: less than 5%, 2: 5-30%, 3: greater than 30%) and the level of concentration of the agent in the work environment (1: low, 2: medium, 3: high). The concentration was assessed with reference to benchmarks specific to each substance. For arsenic, the medium exposure benchmark was considered to be the Threshold Limit Value, which was 0.2 mg/m³, with low and high representing substantially lower and higher values (<0.1 and >1.0 mg/m³, respectively). The dates at which each job started and ended were recorded. Neither interviewers nor chemists were aware of the patient's medical condition when assigning the exposure codes, thus eliminating one potential source of bias.

Occupational exposure to arsenic

One item on the checklist was "arsenic compounds", which comprised arsenic dust, arsenic fumes, dust from arsenic-containing alloys and ores and all other arsenic-containing substances (e.g., calcium, sodium and lead arsenate). Although use of the metal is limited to a few applications involving lead-arsenic alloys, several compounds have been widely used as insecticides. The smelting and refining of arsenic-containing ores (e.g., copper smelting and refining) and boiler cleaning (ashes and soot may contain arsenic trioxide) are other potential sources of exposure.

The Montreal area has little ore smelting or refining. While there is virtually no agricultural activity within the study area boundaries, many men living there had at some time in the past lived and worked in surrounding agricultural areas.

Defining exposure groups for analysis

Since the exposures of interest took place in the past, often decades earlier, direct validation was not possible. For our purposes, the exposure to each substance was defined using dimensions described above (confidence, concentration, frequency) plus duration as follows: (i) unexposed; (ii) possible, when confidence is "possible", or the

Exposure Pattern*	All Subjects (%)†	Lung Cancer Cases (%)‡	Population Control (%)¶	Cancer Control (%)§
Total number	2750	857	533	1360
Unexposed	2627 (95.5)	816 (95.2)	503 (94.4)	1308 (96.2)
Exposed	123 (4.5)	41 (4.8)	30 (5.6)	52 (3.8)
Confidence level††				
Possible	21 (0.8)	10 (1.2)	5 (0.9)	6 (0.4)
Probable	46 (1.7)	14 (1.6)	8 (1.5)	24 (1.8)
Certain	56 (2.0)	17 (2.0)	17 (3.2)	22 (1.6)
Frequency††				
< 5% of work week	49 (1.8)	12 (1.4)	14 (2.6)	23 (1.7)
5-30% of work week	64 (2.3)	26 (3.0)	14 (2.6)	24 (1.7)
> 30% of work week	10 (0.4)	3 (0.4)	2 (0.4)	5 (0.4)
Concentration††				
Low	59 (2.1)	21 (2.5)	12 (2.2)	26 (1.9)
Moderate	54 (2.0)	16 (1.9)	15 (2.8)	22 (1.6)
High	10 (0.4)	4 (0.4)	3 (0.6)	4 (0.3)
Duration				
< 10 years	59 (2.1)	19 (2.2)	13 (2.4)	27 (2.0)
11 - 20 years	21 (0.8)	6 (0.7)	8 (1.5)	7 (0.5)
> 20 years	43 (1.6)	16 (1.9)	9 (1.7)	18 (1.3)
Era of first exposure				
Before 1950	81 (2.9)	25 (2.9)	21 (3.9)	35 (2.6)
1950 - 1960	29 (1.1)	11 (1.3)	4 (0.8)	14 (1.0)
Post 1960	13 (0.5)	5 (0.6)	5 (0.9)	3 (0.2)

* See Methods section for description of confidence, frequency and concentration scales.
† Proportions use 2750 as denominator.
‡ Proportions use 857 as denominator.
¶ Proportions use 533 as denominator.
§ Proportions use 1360 as denominator.
†† For men who were exposed to arsenic in multiple jobs, the confidence, frequency and concentration levels were computed as time-weighted averages of these parameters across the different jobs.

Cancer Controls	Population Controls
<ul style="list-style-type: none"> dust of excavation; brick; coal; metallic; aluminum alloy; copper; mild steel (dust*) fume of arc welding; soldering; copper; lead; zinc; and other pyrolysis acetic acid aliphatic alcohols alkanes (C5-C17) amphibole asbestos calcium oxide chrysotile asbestos copper compounds crystalline silica (C. silica) chromium compounds liquid fuel combustion products lubricating oils and greases monocyclic aromatic hydrocarbons natural gas combustion products (gas) 	<ul style="list-style-type: none"> dust of inorganic insulation; coal; aluminum alloy (dust*) fume of arc welding; gas welding; metallic; calcium oxide; iron; and other pyrolysis aliphatic alcohols ammonia crystalline silica chromium compounds copper compounds engine emissions iron compounds inorganic acid solutions liquid fuel combustion products leaded gasoline lubricating oils and greases monocyclic aromatic hydrocarbons nickel compounds unsaturated aliphatic hydrocarbon

* Dust and fume variables for each set of controls was comprised of those dusts or fumes which individually satisfied the criterion for a potential confounder in the stratified analysis.

exposure occurred within 5 years before the diagnosis of lung cancer or (for controls) entry into the study; (iii) low/moderate, when the exposure occurred at least 5 years preceding the diagnosis, but either accumulated for less than 5 years or the product of concentration times frequency

was less than or equal to 3; and (iv) substantial, when the exposure occurred at least 5 years preceding the diagnosis of lung cancer, accumulated for 5 or more years, and had a frequency times concentration product greater than 3. Initially, groups (iii) and (iv) were collapsed because

TABLE III

Arsenic Exposure and Lung Cancer Risk, Final Models of Logistic Regression Analyses, Using Categorized Smoking Index and Any Exposure vs. No Exposure for Arsenic and all other Chemicals

Control Group	Variable	Odds Ratios (95% Confidence intervals)	
Cancer Controls	Arsenic*	1.1	(0.60 - 1.7)
	Acetic acid	0.81	(0.48 - 1.4)
	Dust	1.4	(1.1 - 1.7)
	Ethnic†	1.2	(1.0 - 1.5)
	Proxy	1.7	(1.3 - 2.1)
	Family income	1.6	(1.3 - 2.1)
	Smoking index‡		
	1-500	4.3	(2.3 - 8.1)
	501-1000	9.4	(5.2 - 16.8)
	1001-1500	12.6	(7.0 - 22.7)
	≥ 1501	25.9	(14.4 - 46.8)
Population Controls	Arsenic	0.82	(0.41 - 1.6)
	Acetic acid	0.79	(0.38 - 1.6)
	Aliphatic alcohol	0.71	(0.48 - 1.1)
	Alkanes	1.7	(1.2 - 2.2)
	Copper compound	1.2	(0.85 - 1.8)
	Liquid fuel	1.2	(0.71 - 2.0)
	Lubricating oil	0.73	(0.54 - 0.98)
	Proxy	3.1	(2.2 - 4.3)
	Family income	1.8	(1.3 - 2.4)
	Smoking index		
	1-500	4.1	(2.1 - 8.1)
	501-1000	11.4	(6.1 - 21.4)
	1001-1500	17.0	(9.0 - 32.1)
	≥ 1501	33.4	(17.5 - 63.7)

* Any exposure vs. no exposure

† Coding for sociodemographic factors: Ethnic (1=French, 2=others); Family income (1 if < \$29,755, 0 if ≥ \$29,755 Canadian dollars); Marital status (1=married, 0=others); Proxy (interviewee status, 1=proxy, 0=self)

‡ Smoking index is equal to number of cigarettes smoked per day times years of smoking

of small numbers, and for the final models, groups 2-4 were collapsed.

Analytic strategy

The main objective was to estimate the odds ratio (OR) between arsenic and lung cancer, controlling for confounders, including other occupational exposures. All analyses were carried out separately using cancer controls and population controls.

Assessment for Confounders and Effect Modifiers

Non-occupational covariates included in the final analyses based on a priori considerations (e.g., consistency with earlier analyses), were: age, ethnic group, family income, marital status, education, cigarette smoking, and an index of "blue collariness" of the job history. Because we had information on hundreds of occupational covariates, we had to reduce the number of variables before conducting multiple regression analyses. The first stage was an empirical search for effect modifiers and confounders. ORs were computed for

arsenic exposure and lung cancer stratified by age and each of the other occupational exposures. If stratum-specific ORs differed substantially, this variable was considered an effect modifier and retained for modeling. Otherwise, it was evaluated as a potential confounder according to a previously described strategy;¹⁵ variables qualified if the confounding ratio (= crude OR divided by the Mantel-Haenszel OR adjusted for that covariate) was greater than or equal to 1.10 (or less than or equal to 1.10⁻¹). These analyses were conducted separately for population-based controls and for cancer controls, leading to different sets of covariates for the modeling analyses.

Logistic Regression Analyses

Logistic regression was used to assess the arsenic/lung cancer association, adjusted for multiple confounders. The initial model included arsenic compounds, non-occupational covariates listed above, job exposures identified by the above strategy; and product terms for arsenic times the potential effect modifiers.

Model-building proceeded by stepwise elimination. First, product terms were eliminated if the Wald test or log likelihood difference resulted in a p-value greater than 0.2. Next, other covariates were eliminated if their removal did not change the arsenic coefficients by more than 15%. Finally, sensitivity analyses, using different codings for chemical exposure (e.g., dichotomous, or level of exposure) or for smoking index, were performed to evaluate robustness of the observed relationship between arsenic exposure and lung cancer.

RESULTS

Overall, about 5% of study subjects were classified as exposed to arsenic compounds, with 5% in cases, 4% in cancer controls, and 6% in population controls. Table I describes the lifetime exposure pattern for arsenic as coded by our chemists, among study subjects. Arsenic exposure was coded in a limited range of occupations, the main one being agricultural work, which accounted for nearly half of those exposed. The source was arsenate pesticides used locally during the 1930s, 1940s and 1950s, with potentially high exposures that would have been short due to the short growing season. Another group with brief but potentially intense exposure was firefighters, who accounted for 14% of arsenic-exposed subjects. Exposure would have resulted from burning wood that had been treated with an arsenic compound. The confidence level for attribution of exposure to this group was generally low. Two other groups were coded as having arsenic exposure with low confidence: stationary engineers from arsenic in small quantities in fossil fuels, and tannery workers from the use of arsenic trisulfide in the unhairing of pelts. A small group of copper refinery workers were ascribed medium to high concentrations and high frequencies. Overall only 2% of the study subjects were considered definitely exposed, and of these, 50% had substantial arsenic exposures. Most men who were coded as exposed had a considerable duration (on average, 16 years) of exposure and an initial exposure before 1950, long enough ago for a reasonable latency period to have elapsed.

The results of empirical screening for confounders are shown in Table II. A somewhat different list emerged for cancer controls as opposed to population controls.

The final logistic regression models are in Table III. The ORs for arsenic exposure and lung cancer were 1.1 (95% confidence interval = 0.60, 1.7) using cancer controls, and 0.82 (95% confidence interval = 0.41, 1.6) using population referents. There was thus no apparent association between arsenic exposure and lung cancer. The overall findings of no interaction on a multiplicative scale between arsenic and smoking (data not shown) is consistent with the synergistic joint effect observed in several studies.¹¹

DISCUSSION

Previous epidemiological evidence demonstrating arsenic's lung carcinogenicity has come from cohort studies, primarily conducted on refinery workers. Preliminary analysis of the Montreal data showed no association (OR = 1.0) between arsenic exposure and lung cancer.¹³ In light of arsenic's well-known human carcinogenicity, one possible explanation for that finding was negative confounding from other workplace chemicals.¹³ However, in this re-analysis of the Montreal data, thorough control for possible confounding effects from other chemicals did not alter the results, despite several strengths. These included a large population, high quality cancer diagnosis (pathologically confirmed cancer diagnoses rather than the error-prone death certificate diagnoses), ability to collect lifetime job histories (rather than just those at one industry or one employer) and to control for multiple occupational exposures, opportunity to adjust for lifestyle confounders (frequently not possible in retrospective occupational cohort studies), and use of two control groups. Although the final logistic regression model included only a handful of factors, our strategy effectively ruled out confounding from the variables collected. Of course, there are practical limitations to this ideal. Variables not collected or collected with error could cause bias in any direction.¹⁹

We carried out parallel analyses using cancer controls and population controls.

The analysis using the cancer controls could be downwardly biased if other cancer sites were also causally related to arsenic exposure. Skin, kidney and bladder cancer have been associated with ingestion of arsenic through naturally contaminated water,^{20,21} but since occupational studies of arsenic exposure through inhalation do not indicate increased risk at those other sites, it is doubtful that attenuation of the ORs occurred as a result of an inappropriate control series. Our results were very similar irrespective of control group, increasing confidence that the findings were not biased by inappropriate controls.

Since arsenic is well established as a human carcinogen by inhalation, our inability to replicate the association must reflect inadequacies in the present study. What were these?

First, although considerable resources were devoted to the retrospective assessment of exposure, the codings were expert judgements, not objective measures. No measurements were available for the subjects or time period of interest, and the hygiene literature on which our evaluations were based was sparse. Consequently, exposure was undoubtedly misclassified for some workers, which for reasons described below would have entailed erroneous categorization of unexposed persons as exposed, i.e., low specificity, leading to a bias of the ORs towards the null.²² Second, the number of subjects with arsenic exposure was small; this low prevalence of exposure resulted in low power to detect risks. Thus, we may have pushed the limits of population-based case-control methodology with the rarity of this exposure. As indicated by the confidence intervals on the ORs, we cannot exclude the possibility of small to medium excess risks. Third, the types of arsenic compounds to which our study subjects were exposed may have differed from those of previously studied workers, and this difference could be related to carcinogenic potential. Fourth, the level of arsenic exposure may have been so low that any true effect would have been too small to be detectable. For several reasons, we believe this last weakness is the major reason for our null findings.

In this study, about half of the participants with arsenic exposure were farmers,

and arsenic exposure was mainly from using arsenic-containing pesticides. In an early study of the health effects of exposure to lead arsenate,²³ orchardists in Washington state who burned insecticide containers were exposed to the highest concentration of arsenic in the air (4.86-26.12 mg/m³, average=16.67 mg/m³), followed by those who mixed the insecticide (0.02-11.07 mg/m³, average=1.85 mg/m³), and by those who picked fruits (0.26-1.9 mg/m³). In a cohort study of mortality among orchard workers in this same cohort exposed to lead arsenate spray,²⁴ orchardists had higher mean levels of urinary arsenic when compared to adult consumers and children, but no excess cancer mortality. Their exposure levels are comparable to concentrations observed in smelters, where excess lung cancer mortality has been repeatedly observed,⁴⁻⁶ e.g., at time-weighted average arsenic exposure levels of 7.03 mg/m³ or greater.⁶ However, the frequency of arsenic exposure in orchardists or farmers would be much less than that of smelter workers. The farmers in this study generally applied pesticides 3-4 times a year due to the short growing season in Quebec. Each application may have been completed in a few days and the peak exposures may have been for only a fraction of each day, particularly since these activities occurred out of doors. For smelter workers, arsenic exposures were continual, generally occurring every work day, throughout much of the day, indoors. Thus, even with comparable air concentrations, the cumulative exposures may have differed by orders of magnitude, e.g., easily as much as 100-fold. The lack of any quantification of exposure also leaves open the possibility that even at the times of infrequent exposure, the levels were small or even negligible, which if true, would seriously reduce the possibility of observing an elevated risk. This study therefore may provide a further example of the importance of dose in resolving discrepancies among studies.²⁵

In summary, this population-based case-control study found no association between arsenic exposure and lung cancer mortality after thoroughly controlling for other occupational factors. In light of an abundant and convincing literature that

establishes arsenic exposure via inhalation as a human lung carcinogen, the discrepant findings in this study are most likely a result of lower exposure levels in these subjects. Other factors that may have contributed to these null findings include: different speciation of arsenic compounds in the exposures of these subjects; exposure misclassification in this study, since the assessment was based on interviews combined with expert assessments but not workplace measurements; and low power because of small numbers exposed. These findings underscore (a) the limitations of population-based case-control studies when exposures are rare; (b) the need for caution in interpreting negative findings from studies with rare or low-level exposures; (c) the reduced utility of the population-based design for hypothesis generation of putative carcinogens or other toxins.

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