Reducing aluminum: an occupation possibly associated with bladder cancer

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A case–control study, undertaken to identify reasons for the exceptionally high incidence of bladder cancer among men in the Chicoutimi census division of the province of Quebec, revealed an increased risk associated with employment in the electrolysis department of an aluminum reduction plant. The estimated relative risk was 2.83 (95% confidence interval: 1.06 to 7.54). An interaction was found between such employment and cigarette smoking, resulting in a combined relative risk of 5.70 (95% confidence interval: 2.00 to 12.30). These findings suggest that employment in an aluminum reduction plant accounts for part of the excess of bladder cancer in the region studied.

Une étude épidémiologique de type cas/témoin fut conduite dans le but de trouver les raisons pouvant expliquer la présence d'un excès de cancers de la vessie chez les hommes de la division de recensement de Chicoutimi, province de Québec. Les résultats montrent qu'il y a plus d'hommes qui ont travaillé au département d'électrolyse d'une industrie d'aluminium parmi les patients que parmi les témoins. Le risque relatif estimé associé au travail dans l'aluminium est de 2.83 (intervalle de confiance 95%: 1.06 à 7.54). Ce risque relatif s'élève à 5.70 (intervalle de confiance 95%: 2.00 à 12.30) pour ces travailleurs qui fument la cigarette, ce qui indique une interaction entre ces deux expositions. Ces résultats suggèrent que le travail dans l'industrie de réduction de l'aluminium explique en partie l'excès de cancer de la vessie noté dans la région étudiée.

The mapping of cancer incidence in Canada according to county in 1969–72 revealed an area along the Saguenay River in the province of Quebec where the rates for bladder cancer were exceptionally high among men.[1] To identify reasons for these high rates we conducted a case–control study of bladder cancer diagnosed among residents of the Chicoutimi census division.

Methods

Cases of bladder cancer among residents of the Chicoutimi census division diagnosed between 1970 and 1975 were identified from two sources: the Province of Quebec Tumor Registry and the records of Chicoutimi Hospital. The tumours were classified according to Jewett[2] after a pathologist had reviewed the reports.

The controls were neighbours matched by age and sex whose residence was closest to the patients' at the time of diagnosis. They were identified from the list of persons registered in each patient's electoral district. Looking at addresses on the same side of the street as the patient's but with increasingly higher numbers, we chose the first person who was of the same sex and within the same 5-year age bracket. When no such person was found we looked at addresses on the other side of the street. If we still could not find a matched control we looked at decreasing address numbers on the same side of the street and then the other side.

Locally hired interviewers, supervised by two coordinators, a physician and a public health nurse, conducted personal interviews with the patients and controls, or the next of kin if the subject had died. At the time of the interview the interviewers did not know if the questioned person was a patient or a control. The questionnaires included questions about other diseases (so as not to emphasize bladder cancer) and cross-checking questions (to control for information about pertinent exposure). All completed questionnaires were reviewed by the coordinators.

Information was obtained on place, type and length of employment for all jobs held. The respondents were asked to describe the duties performed in each job, as well as to list the materials handled during the course of their work. The occupational section of the questionnaire concluded with a review of industries, occupations and materials known to be associated with bladder cancer. The same questions applied to other occupations and hobbies. Data were also collected on the past medical history, residential history, consanguinity of parents, consumption of coffee, analgesics, artificial sweeteners, alcohol and untreated drinking water, and smoking habits.

Results

A total of 96 patients with bladder cancer and 96 controls were identified. Interviews were completed for 91 pairs; four persons refused to answer the questionnaire and one could not be retraced. The patients included 81 men and 10 women; the sex ratio, 8.1, differed significantly ($P < 0.01$) from that for bladder cancer in the province of Quebec, 3.5.[3] The results presented in this paper are thus restricted to those for the men.

The observed numbers of cases of bladder cancer were significantly higher ($P < 0.05$) than the expected numbers for the men aged 45 to 74 years (Table I). The mean age of the patients was significantly lower ($P < 0.01$) than expected (Table I).

An analysis of place of residence did not reveal any recent migration to the study region from adjacent regions that might explain the increased incidence of bladder cancer.

There was no significant difference between patients and controls in the frequency of several confounding variables: consanguinity of parents, a history of disease of the urinary tract, and consumption of certain drugs, artificial sweeteners, alcohol and untreated drinking water (Table II). Bladder stones were reported by seven patients but only three controls. Further differen-

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tiation as to type and quantity of alcohol consumed was not informative.

There were no differences in coffee consumption (number of coffee drinkers, quantity and duration of coffee intake or type of coffee [instant, decaffeinated or bean]) between the patients and the controls (Table III).

The numbers of smokers and the average number of cigarettes smoked per day did not differ between the patient and control groups, but the average number of years of smoking was slightly greater for the patients (Table IV).

The main findings pertained to employment. Although there were no differences between patients and controls in the types of industries they were ever employed in (Table V) or in their exposure to potentially carcinogenic chemicals (Table VI), there was a difference in occupation within the aluminum industry: working in the electrolysis department of an aluminum plant at some time during working life was reported by 25 patients but only 14 controls (Table VII). There was a tendency for the patients to have worked longer than the controls in that particular area (Table VIII).

The McNemar chi-square test, applied to paired patients and controls, confirmed the presence of a significant association between bladder cancer and exposure to the aluminum reducing process, with an estimated relative risk of 2.83 (Table IX). The risk of bladder cancer for cigarette smokers and the risk for workers in the electrolysis department of an aluminum plant were of the same magnitude, but the two factors had an additive effect that tended toward synergism, although it was not statistically significant (Table X).

Discussion

Bladder cancer has been associated with cigarette smoking,[7-14] several occupations[15-19] and exposure to various chemicals, such as 4-aminobiphenyl, β-naphthylamine, benzidine and 4-nitrobiphenyl.[20-22] The role of artificial sweeteners in the development of bladder cancer in humans has been more controversial.[23-26] Drugs such as antipyrine (phenazone) and phenacetin,[27] cyclophosphamide[28] and azathioprine[29] were consumed by people in whom bladder cancer has developed. Coffee is a suspected bladder carcinogen in humans.[30-33]

Predisposing factors for bladder cancer are believed to be urinary stasis,[34] the presence in the bladder of parasites[35] or stones[36] and the drinking of water containing nitrates when one has a urinary tract infection.[37,38] The existence of families with a high incidence of bladder cancer and no exposure to known carcinogens has raised the possibility of genetic transmission of the disease.[39-41]

The results of our study raise the possibility that bladder cancer is associated with working in the electrolysis department of an aluminum plant. To make sure that the excess number of cases was not attributable to a bias from next-of-kin reporting, we compared the occupational history in the 47 pairs who were still alive and answered the questionnaire personally. Because 17 patients and 7 controls had worked in the electrolysis department of an aluminum plant the significant association between bladder cancer and work in such

Table I—Observed and expected cases of urinary bladder cancer diagnosed between 1970 and 1975 in men in the Chicoutimi census division, by age

Age (yr)	No. of cases: Observed	No. of cases: Expected*	Ratio, observed : expected
25–34	1	0.69	1.45
35–44	4	1.70	2.35
45–54	18	6.36	2.83‡
55–64	24	14.66	1.64‡
65–74	25	15.88	1.57‡
75+	9	9.23	0.97
Total	81	48.52	1.67‡
Mean† ± standard deviation (SD), yr	61.6 ± 11.8	65.5	

*Based on age-specific incidence rates of bladder cancer in Quebec, as estimated from data from the Province of Quebec Tumor Registry.
†Difference significant by a two-tailed t-test for unpaired data: $t = 2.97$; $P < 0.01$.
‡Significant at $P < 0.05$.[4]

Table II—Frequency of several confounding variables in the patient and control groups of men

Variable	No. of men: Patients (n = 81)	No. of men: Controls (n = 81)
Reported kinship of father and mother	3	4
Previous urinary tract disease	22	19
Consumption of caffeine, phenacetin and other analgesics	7	4
Artificial sweeteners	3	3
Alcohol	45	46
Untreated drinking water	56	57

Table III—Coffee consumption of the men

Variable	Patients (n = 81)	Controls (n = 81)
Coffee drinkers, no.	61	60
Weekly intake of coffee, mean no. of cups ± SD	17.2 ± 13.6	15.6 ± 19.9
Years of regular intake of coffee, mean no. ± SD	32.4 ± 16.9	33.9 ± 17.0

Table IV—Smoking habits of the men

Variable	Patients (n = 81)	Controls (n = 81)
Smokers, no.	65	59
Cigar or pipe smoking only, no.	10	6
Cigarettes per day, mean ± SD	23.5 ± 10.3	24.1 ± 16.7
Years of smoking, mean* ± SD	42.9 ± 16.4	36.7 ± 16.6

*Difference between the groups significant by a two-tailed t-test for unpaired data: $t = 2.0$; $P < 0.05$.

an area persisted (relative risk 3.50; 95% confidence interval 1.11 to 11.08).

Although this occupation has not been associated with bladder cancer in the past, such a finding is not surprising since, in the aluminum reduction process, fumes and gases containing aromatic amines and polycyclic aromatic hydrocarbons and their byproducts are released into the workplace.[1,42] These carcinogenic chemicals could well contribute to the development of bladder cancer in aluminum workers.

In our subjects the association between working in the electrolysis department of an aluminum plant and bladder cancer in those who did not smoke (relative risk 1.90) was not much greater than the association between cigarette smoking and bladder cancer (relative risk 1.82). There was, however, an interaction of the two factors, so that persons who had that occupation and smoked cigarettes had a much higher relative risk (5.70). A similar synergism of cigarette smoking and exposure to carcinogens in cancer production has previously been observed.[43,44]

The Chicoutimi census division, where the high incidence of bladder cancer was observed, is a remote area with a population of 163 350 (in 1971).[45] Most people are of Canadian origin and 96.7% are French speaking.[46,47] Of the male work force 37.9% are employed

Table V—Industries the men were ever employed in and mean duration of employment

Industry	Patients n	Patients Mean duration ± SD (yr)	Controls n	Controls Mean duration ± SD (yr)
Farming	9	22.3 ± 23.9	12	24.7 ± 19.6
Farming aid	16	14.4 ± 5.7	14	17.8 ± 6.0
Lumber	27	17.0 ± 13.2	26	11.7 ± 8.9
Pulp and paper	18	18.6 ± 16.5	19	19.0 ± 16.2
Aluminum	44	22.4 ± 12.5	38	22.8 ± 14.3
Petroleum	7	15.4 ± 14.5	8	12.8 ± 10.4
Construction	19	11.7 ± 16.9	20	19.7 ± 18.8
Road, transportation	14	13.3 ± 12.5	18	13.4 ± 12.7
Trade	17	17.6 ± 17.0	19	15.5 ± 14.3
Professional and others	13	17.5 ± 14.9	17	17.5 ± 17.8

Table VI—Exposure of the men to potentially carcinogenic chemicals

Chemicals	No. of men: Patients	No. of men: Controls
Solvents	9	9
Paints	10	7
Dyes	5	1
Chemicals	18	11
Leather	4	0
Pigments	0	2
Tar or pitch	14	12
Pesticides	0	2
Insecticides	1	2
At least one of the above	35	34
No exposure	46	47

Table VII—Occupations suspected of exposing the worker to bladder carcinogens

Occupation	No. of men: Patients	No. of men: Controls
Photography	0	1
Painting	7	6
Garment making	0	0
Hairdressing	0	0
Laboratory work	0	1
Aluminum electrolysis work*	25	14
Farming	25	26
At least one of the above	42	39
None	39	42

*Difference between the groups significant by the chi-square test: $\chi^2_1 = 4.09$; $P < 0.05$.

Table VIII—Number of years spent in the electrolysis department of an aluminum plant

No. of years*	No. of men: Patients (n = 25)	No. of men: Controls (n = 14)
1–9	5	5
10–19	1	3
20–29	9	2
30+	10	4

*Difference between the patients and controls, grouped by number of years in the electrolysis department, significant by the chi-square test: $\chi^2_1 = 4.28$; $P < 0.05$.

Table IX—Matched pairs analysis of the association between bladder cancer and exposure to aluminum reduction

No. of controls	No. of patients: Exposed	No. of patients: Not exposed
Exposed	8	6
Not exposed	17	50

Estimated relative risk: 2.83*
95% confidence interval: 1.06 to 7.54

*A relative risk is said to be significant when its confidence interval does not include the value 1.0. In this case the McNemar χ^2 value was 4.34.

Table X—Relative risk of bladder cancer in the cigarette smokers and the workers in the electrolysis department of an aluminum plant

Work in electrolysis department	Cigarette smoking: Never or in the past	Cigarette smoking: Current
No	1.00	1.82
Yes	1.90	5.70

Relative risk: 1.00 for people who never worked in the electrolysis department of an aluminum plant and who stopped smoking (there were no nonsmokers in the electrolysis department).
95% confidence intervals according to Miettinen:[5]
Cigarette smokers: 0.78 to 4.32
Aluminum workers: 0.51 to 7.00
People with simultaneous exposure to the two factors: 2.00 to 12.30
95% confidence interval for synergistic effect according to Rothman:[6]
0.43 to 16.44 ($\hat{S}$[Rothman's index of synergy] = 2.67)

in manufacturing.[48] In 1971 the male labour force in the Chicoutimi–Jonquière metropolitan census area was estimated at 28 100.[49] About 4935 men were employed in aluminum smelting, refining and rolling. Assuming that 50% of the aluminum workers were assigned to the electrolysis department, and knowing from the control group that 50% of these workers would be nonsmokers or ex-smokers, we can estimate by calculating attributable risks[50] that 21% of the cases of bladder cancer in the Chicoutimi area were related to exposure to aluminum electrolysis (Table XI). This would account for 53% of the excess cases of bladder cancer reported in this region.

Further studies of workers in the aluminum reduction industry should help quantify the risk of bladder cancer and identify the chemicals responsible for its development.

We are indebted to the staff of Chicoutimi Hospital, especially Drs. P. Desmeules, A. Fernet and L. Privé, for access to data, to Drs. J. Fabia, M. Plante, J.P. Leclerc and D.T. Wigle and Mr. P.M. Bernard for advice and support, to Dr. J.M. Fredette, Mr. R. Rémillard and Mrs. G. Thibault for access to the Province of Quebec Tumor Registry, and Mrs. J.A. Harvey, M.C. Bobée and A. Lambert for their technical and clerical assistance.

This project was supported in part by National Health Research and Development Project 605-1387-40 of the Department of National Health and Welfare.

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Table XI—Estimation of risk of bladder cancer attributable to exposure to the aluminum reduction process

Type of exposure	Estimated relative risk	% of population exposed	Attributable risk (%)*	No. of cases attributable
Aluminum reduction process only	1.90	4.4	3.8	3.1
Aluminum reduction process and cigarette smoking	5.70	4.4	17.1	13.9
Total			20.9	17.0

*Calculated as follows: $p(r-1) \div [p(r-1)-1]$, where p = proportion exposed and r = relative risk.

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