# Exhibit 310

# Surveillance of nasal and bladder cancer to locate sources of exposure to occupational carcinogens

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**Abstract**

***Objective*—To locate sources of occupational exposure to nasal and bladder carcinogens for surveillance follow up in British Columbia, Canada.**

***Methods*—Incident cases of nasal cancer (n=48), bladder cancer (n=105), and population based controls (n=159) matched for sex and age, were interviewed about their jobs, exposures, and smoking histories. Odds ratios (ORs) were calculated for 57 occupational groups with stratified exact methods to control for age, sex, and smoking.**

***Results*—Occupational groups at increased risk of nasal cancer included: textile workers (six cases, OR 7.6); miners, drillers, and blasters (six cases, OR 3.5); welders (two cases, OR 3.5); pulp and paper workers (three cases, OR 3.1); and plumbers and pipefitters (two cases, OR 3.0). Nasal cancer ORs were not increased in occupations exposed to wood dust, possibly due to low exposures in local wood industries. Strongly increased risks of bladder cancer were found for sheet metal workers (four cases, OR 5.3), miners (19 cases, OR 4.5), gardeners (six cases, OR 3.7), and hairdressers (three cases, OR 3.2). Among occupations originally considered at risk, the following had increased risks of bladder cancer: painters (four cases, OR 2.8); laundry workers (five cases, OR 2.3); chemical and petroleum workers (15 cases, OR 1.8); machinists (eight cases, OR 1.6); and textile workers (three cases, OR 1.5).**

***Conclusions*—Occupational groups with increased risks and three or more cases with similar duties were selected for surveillance follow up. For nasal cancer, these included textile workers (five were garment makers) and pulp and paper workers (three performed maintenance tasks likely to entail stainless steel welding). For bladder cancer, these included miners (12 worked underground), machinists (five worked in traditional machining), hairdressers (three had applied hair dyes), and laundry workers (three were drycleaners).**

(*Occup Environ Med* 1997;54:443–451)

Keywords: textile industry; paper; wood; mining; occupational exposure

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Accepted 18 December 1996

Traditional disease surveillance has used vital statistics data bases to examine patterns of mortality in occupations and industries and generate hypotheses for further epidemiological study.[1] After the definition by Rutstein *et al*[2] of occupational sentinel health events, many recent surveillance efforts have aimed to provide a more direct impetus to action, including treatment of patients, screening for disease in coworkers, and investigations into industrial hygiene at associated work sites.[3] Few such studies have investigated cancer outcomes,[4–6] although 13 cancers are listed as occupational sentinel health events.[2] There may be several reasons.

Cancers have long induction and latent periods, so sources of exposure may no longer exist by the time the case is identified. Although this will often be true, recent studies of mesothelioma led to the discovery of previously unrecognised current sources of exposure to asbestos.[5] This is especially important evidence of the potential value of cancer surveillance, as asbestos is one of the best known industrial hazards of this century. Sources of other carcinogens are likely to be less well recognised.

Studies that followed the sentinel event approach of Rutsein *et al* have identified case series, then used case by case evaluations to assess the relation of a disease event to work.[3 4 6] The ability to assess aetiology on an individual basis was a criterion for selecting diseases for the United States sentinel event notification system for occupational risks (SENSOR).[3] For cancer, and most other diseases on the sentinel events list, it would be difficult to attribute cause on an individual basis, as most cancers with occupational aetiologies also occur in the absence of such exposures. Surveillance would require analytical methods which compare groups.

We conducted a surveillance study of three cancer types, mesothelioma, nasal cancer, and bladder cancer, with case-control methodology. It was designed to locate sources of occupational exposure to known or probable carcinogens in the province of British Columbia, Canada, with the aim of alerting regulatory agencies and industrial health professionals about occupations that warranted occupational hygiene exposure measurement, and control. This paper reports the results for nasal and bladder cancer, both of which have several known occupational aetiologies, as well as non-industrial aetiologies, in particular, smoking. The results for mesothelioma are reported elsewhere.[7]

## Materials and methods

### IDENTIFICATION OF CASES

All incident cases with histologically confirmed primary malignant tumours of the nasal cavity or sinuses (ICD-O topography codes 160.0 and 160.2 to 160.9), and urinary bladder (ICD-O 188) age ≥19 and registered by the British Columbia Cancer Agency (BCCA) were considered eligible for the study. The registry of the BCCA is population based and for case ascertainment uses reports from all provincial pathology and haematology laboratories, death notices from the British Columbia Division of Vital Statistics, reports from other Canadian registries about cancers in residents of British Columbia, and admission records from BCCA clinics. A BCCA pathologist, not blinded to the initial diagnosis, reviewed tissue samples for every case initially identified as eligible.

The study period was 1 September 1990 to 31 August 1992 for nasal cancer, to allow accrual of about 50 cases, and 1 September 1990 to 31 May 1991 for bladder cancer, sufficient for accrual of at least 100 cases. As people with an industrial background have often been found to develop bladder cancer at younger ages than those with other backgrounds,[8–10] cases of bladder cancer were restricted to those born after 31 December 1915.

### SELECTION OF CONTROLS

Controls were randomly selected from five-year age and sex strata of the provincial voters list updated to 17 July 1991. Those eligible included all residents of British Columbia who were Canadian citizens aged ≥19 and who were not in prison or confined to a mental health institution by court order. Controls were frequency matched to the age and sex distribution of cases of all three types of cancer included in the study. All study controls within two years of age of the cases were included in the analyses for each cancer site.

### INTERVIEWS

The methods of contacting subjects in this study were reviewed and approved by the University of British Columbia Behavioural Sciences Screening Committee. All subjects living within about six hours surface travel time of Vancouver (one way) were interviewed either in person or by telephone, at their convenience. The remaining interviews were conducted by telephone (21% for cases and 23% for controls).

If a subject did not speak English well or had trouble recalling events in his or her life, a relative chosen by the subject was asked to translate or help with the interview. If the subject was dead, the surviving next of kin who had most recently lived with the subject was contacted for interview. An attempt was made to frequency match next of kin control interviews to the number of next of kin case interviews within age-sex strata. However, when no next of kin was available or the request for a next of kin interview would have resulted in a refusal, the interview was conducted with the control instead.

Interviews were conducted with a standardised questionnaire based on a prototype originally developed by the United States National Cancer Institute to investigate occupational associations with mesothelioma.[11] It included occupational, residential, smoking, and medical histories, and an exposure history aimed at identifying exposures considered by the International Agency for Research on Cancer (IARC)[12–16] to be known or probably carcinogenic. Interviews were conducted with a standardised questionnaire. For this study, questions about specific exposures and work processes relating to nasal and bladder cancer were added. An interview guide was used to aid recall of exposure; it listed types and trade names of products in which carcinogens were used. Data for the interview guide was obtained from the Canadian Centre for Occupational Health and Safety trade names data base, the Canadian Pharmaceutical Society, Health and Welfare Canada, and texts.[17 18]

All interviews were conducted by a registered nurse who was aware of the case-control status of the subjects, but was not aware of aetiologies for the specific cancer sites. All interviews were reviewed for completeness by an industrial hygienist (KT) who was not aware of the case-control status of the subjects. Additional information requested by the hygienist (missing data, or further information to clarify tasks or exposures) was sought by the interviewer.

### OCCUPATIONAL GROUPS

All occupations and industries listed were coded to the fourth digit of the standard occupational and industrial classification.[19 20] In total, 3951 separate jobs were listed by the interviewees, representing over 300 occupational and 500 industrial codes. For analysis, grouping of jobs was necessary. However, collapsing to the third or second digit of the standard classifications was likely to group people with very different exposures (all construction trades together, production and management employees together within an industry), who might be kept separate in a grouping scheme specific to the study.

Such a scheme was therefore developed without knowledge of the case or control status of the people whose jobs were being grouped. When occupation was considered most likely to determine exposures, it was used as the basis for assignment to a group (managers, teachers, truck drivers), and when the industry was judged more likely to determine exposures, such as production and labouring jobs, it was used to assign groups (sawmill workers, railway transport workers). Where both industry and occupation would be expected to determine potential exposures (industrial mechanics, welders, and other tradespeople), occupation was used as the basis for classification.

After the initial assignment to occupational groups, the descriptions of duties and exposures accompanying each job listing were reviewed to ensure the best possible classification—for example, a retail store "manager" who stocked shelves and acted as a

*Table 1 Response characteristics of eligible cases and controls, and characteristics of interviewees*

| | *Nasal cancer* | | *Bladder cancer* | |
|---|---|---|---|---|
| | *Cases* | *Controls* | *Cases* | *Controls** |
| Total eligible: | 54 | 195 | 119 | 173 |
| Physician refusal | 1 | NA | 2 | NA |
| Unable to contact | 0 | 3 | 3 | 3 |
| Case or control refusal | 5 | 33 | 8 | 31 |
| Interview incomplete | 0 | 0 | 1 | 0 |
| Interview complete (% of eligible) | 48 (88.9) | 159 (81.5) | 105 (88.2) | 139 (80.3) |
| Men (%) | 33 (68.8) | 128 (80.6) | 88 (83.8) | 112 (80.3) |
| Age (y, mean(SEM)) | 66.3 (1.9) | 65.5 (0.8) | 64.8 (0.8) | 63.4 (0.8) |
| Next of kin interviewees (%) | 7 (14.6) | 22 (13.8) | 19 (18.1) | 19 (13.7) |
| Never smoked | 11 | 36 | 14 | 31 |
| Ex-smokers | 31 | 88 | 56 | 75 |
| Current smokers | 6 | 35 | 35 | 33 |
| Pack-years (mean(SEM)) | 32.3 (5.5) | 27.3 (2.8) | 38.9 (3.4) | 26.7 (3.0) |

* Controls used in the bladder cancer analysis are a subset of those used in the analysis of nasal cancer; 22 were not included because they were born before 31 December 1915.
NA = not applicable.

cashier was grouped with sales clerks instead of managers; a motor body shop worker who painted cars was grouped with painters, rather than service station attendants or vehicle mechanics. Finally, occupational groups with < 20 listings were reviewed to find whether they could be combined with others. In a few instances, this was not considered possible (hairdressers and barbers, laundry personnel, firefighters). In the final classification, all job listings were assigned to one of 57 occupational groups (table 2).

### CASE-CONTROL ANALYSIS

Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated for "ever" (defined as six months of employment or longer) versus "never" employed in each occupational group. Latency analyses were conducted for all occupational groups, with the most recent 20 years of employment removed. Odds ratios were also calculated for 5, 10, and 15 year latencies for all occupational groups which were originally suspected or which had ORs of ≥2.0 in the initial ever or never analyses. Effect estimates were also calculated for two duration of employment categories: 6 months to < 10 years; and ≥10 years. These are reported when they influence the interpretation of the results.

All OR estimates were adjusted for sex, age (in three strata: < 60; 60 to 69; and ≥ 70), and cigarette smoking. Strata for smoking were based on associations within this dataset for each cancer site, resulting in two strata for nasal cancer (0-19; and ≥20 pack-years), and three strata for bladder cancer (0-9; 10-39; and ≥40 pack-years). Sex-specific analyses (men only) were conducted for ever versus never employed in each occupational group. When these showed notable differences compared with the sex adjusted analyses, further investigations were carried out.

Because of the small size of some occupational groups, exact methods were used to summarise ORs across all strata and calculate 95% CIs.[21 22] All summary ORs and 95% CIs were calculated with Egret (Statistics and Epidemiology Research Corporation, Seattle, WA, 1993).

The ORs and 95% CIs were also calculated for occupational exposures to specific agents and processes, and for other factors—for example, diseases, or drugs—considered to be possibly related to nasal and bladder cancer. When non-occupational factors originally suspected were shown to be positively associated, unconditional logistic regression was used to find whether effect estimates for occupational groups with increased relative risks remained the same after adjustment for these additional potential confounders.

### SELECTION OF OCCUPATIONS FOR SURVEILLANCE FOLLOW UP

A standard framework was used to select which occupations were of interest for surveillance follow up. An occupational group was designated for notification of occupational health personnel if (*a*) it had an OR of > 3.0 in the ever employed analysis, or an OR > 1.2 if it was originally considered to be at risk based on a literature review, and (*b*) at least three cases in the occupational group had a pattern of similar job duties or exposures. Before notification of local regulatory agencies and hygienists, consideration was given to whether the designated jobs were already recognised as associated with cancer in British Columbia. As this final selection process was mainly of local interest, it is not described in detail here.

## Results

### COMPARABILITY OF CASES AND CONTROLS

There were six cases of nasal cancer and 18 cases of bladder cancer initially reported by the BCCA that were found on pathology review not to be eligible for the present analysis. Table 1 indicates the response rates of those considered eligible for the study after pathology review. Information was obtained for 80%–90% of both cases and controls, and in most instances from the subjects themselves.

Table 1 also indicates selected descriptive characteristics of the interviewed subjects. Because the cases of bladder cancer and controls were restricted to those born after 1915, 22 of the controls selected for the overall study were not eligible for the bladder cancer analysis. The mean ages among cases were similar to controls. There were differences in sex distribution between the cases of nasal cancer and controls, because the frequency matching of controls to cases was based on the distribution for all three cancer sites combined and nasal cancer had a higher proportion of female cases than did mesothelioma or bladder cancer.

### NASAL CANCER

Table 2 shows the ORs and 95% CIs of associations between the 57 occupational groups and cancers of the nasal cavity and sinuses. Textile workers had a significantly increased risk in the ever employed analysis. Only one exposed case and two exposed controls were men. Sex specific analyses gave ORs of 3.5 (95% CI 0.1 to 89.3) for men and 12.9 (95% CI 1.3 to 663) for women ever employed. All five female cases and the one

*Table 2 Odds ratios* showing associations between occupational groups and cancer of the nasal cavity or sinuses: all cases (n=48) and controls (n=159) included*

| | *Ever employed* | | | *Most recent 20 years removed* | | |
|---|---|---|---|---|---|---|
| | *Cases/controls n* | *Ever employed OR* | *95% CI* | *Cases/controls n* | *Ever employed OR* | *95% CI* |
| Occupational groups with OR ≥ 3.0: | | | | | | |
| Textile workers | 6/3 | 7.6 | 1.4-56.6 | 4/3 | 5.0 | 0.8-43.0 |
| Miners, drillers, and blasters† | 6/7 | 3.5 | 0.9-14.6 | 6/7 | 3.5 | 0.9-14.6 |
| Welders† | 2/4 | 3.5 | 0.2-53.7 | 2/3 | 3.9 | 0.2-63.4 |
| Pulp and paper mill workers† | 3/3 | 3.1 | 0.4-25.4 | 3/3 | 3.1 | 0.4-25.4 |
| Plumbers and pipefitters† | 2/2 | 3.0 | 0.2-49.1 | 2/2 | 3.0 | 0.2-49.1 |
| Occupational groups originally suspect: | | | | | | |
| Painters | 2/4 | 2.2 | 0.2-17.9 | 2/3 | 2.6 | 0.2-24.8 |
| Machinists† | 3/8 | 1.9 | 0.3-10.6 | 3/7 | 2.1 | 0.3-13.4 |
| Carpenters and wood workers, nec† | 6/27 | 1.0 | 0.3-2.9 | 4/25 | 0.7 | 0.2-2.3 |
| Smelter and foundry workers† | 2/9 | 0.9 | 0.1-5.3 | 2/7 | 1.4 | 0.1-9.8 |
| Chemical and biological laboratory personnel | 2/8 | 0.7 | 0.1-4.0 | 2/7 | 0.9 | 0.1-5.3 |
| Forestry and logging workers† | 2/13 | 0.5 | 0.1-2.4 | 2/12 | 0.5 | 0.1-2.7 |
| Sawmill workers† | 3/22 | 0.4 | 0.1-1.6 | 2/21 | 0.3 | 0-1.4 |
| Shoe and leather workers | 0/6 | 0 | 0-2.8 | — | — | — |
| Other occupational groups: | | | | | | |
| Administrators, managers | 5/22 | 0.7 | 0.2-2.2 | 3/16 | 0.66 | 0.1-2.7 |
| Travelling managers and salesmen | 4/33 | 0.4 | 0.1-1.4 | 4/26 | 0.57 | 0.1-1.9 |
| Accountants, book-keepers | 7/21 | 1.4 | 0.5-4.0 | 6/13 | 1.88 | 0.5-6.1 |
| Engineers, designers† | 0/7 | 0 | 0-4.0 | — | — | — |
| Teachers, librarians | 5/15 | 0.9 | 0.2-3.0 | 5/10 | 1.49 | 0.4-5.4 |
| Sales clerks | 12/41 | 0.9 | 0.4-2.1 | 11/34 | 1.06 | 0.4-2.6 |
| Office clerks and secretaries | 12/27 | 1.2 | 0.4-3.1 | 11/25 | 1.24 | 0.5-3.2 |
| Healthcare workers | 4/9 | 1.3 | 0.3-5.6 | 4/8 | 1.53 | 0.3-6.6 |
| Radio operators | 0/9 | 0 | 0-1.3 | — | — | — |
| Surveyors, prospectors, trappers† | 1/8 | 0.5 | 0-42 | 1/8 | 0.48 | 0-4.2 |
| Warehouse clerks and labourers | 9/35 | 0.9 | 0.4-2.3 | 7/28 | 0.96 | 0.3-2.6 |
| Delivery personnel, unmotorised | 7/37 | 0.6 | 0.2-1.5 | 7/35 | 0.63 | 0.2-1.7 |
| Firefighters† | 2/5 | 1.8 | 0.2-13.4 | 1/5 | 1.02 | 0-11.1 |
| Guards, police† | 3/8 | 1.6 | 0.2-8.0 | 3/2 | 9.19 | 0.9-139 |
| Armed forces personnel, nec† | 10/37 | 1.0 | 0.4-2.4 | 10/37 | 1.0 | 0.4-2.4 |
| Janitors | 3/11 | 1.4 | 0.2-6.3 | 1/8 | 0.5 | 0-4.4 |
| Housekeepers | 8/13 | 1.6 | 0.4-6.7 | 7/12 | 1.5 | 0.4-6.1 |
| Handymen and apartment caretakers | 2/16 | 0.4 | 0.0-2.0 | 0/5 | 0 | 0-3.1 |
| Laundry personnel | 0/4 | 0 | 0-13.9 | — | — | — |
| Hairdressers, barbers | 1/1 | 2.5 | 0-225 | 1/1 | 2.5 | 0-225 |
| Cooks | 4/13 | 0.9 | 0.2-3.0 | 2/10 | 0.7 | 0.1-3.5 |
| Food service personnel | 6/24 | 0.7 | 0.2-2.0 | 6/19 | 1.1 | 0.3-3.2 |
| Food processors | 7/22 | 1.2 | 0.4-3.4 | 6/22 | 1.0 | 0.3-3.0 |
| Farmers and farm labourers | 10/44 | 0.9 | 0.3-2.2 | 10/43 | 0.9 | 0.3-2.3 |
| Gardeners† | 3/4 | 2.9 | 0.4-19.8 | 2/4 | 2.0 | 0.2-16.1 |
| Fishermen† | 0/4 | 0 | 0-6.6 | — | — | — |
| Sheet metal workers† | 1/2 | 2.3 | 0-67.2 | 1/2 | 2.3 | 0-67.2 |
| Chemical and petroleum workers | 1/10 | 0.4 | 0-2.8 | 1/7 | 0.6 | 0-5.1 |
| Construction foremen† | 2/8 | 0.9 | 0.1-5.0 | 2/5 | 1.4 | 0.1-10.1 |
| Construction labourers† | 5/23 | 0.9 | 0.2-2.8 | 4/19 | 0.7 | 0.2-2.3 |
| Bricklayers, plasters, and cement workers† | 1/7 | 0.5 | 0-4.8 | 1/5 | 0.7 | 0-7.7 |
| Electricians and electrical equipment installers† | 0/9 | 0 | 0-3.6 | — | — | — |
| Heavy equipment operators† | 1/7 | 0.5 | 0-4.8 | 0/7 | 0 | 0-2.6 |
| Motor vehicle operators | 10/28 | 1.5 | 0.6-3.7 | 10/24 | 1.9 | 0.7-4.9 |
| Pilots, aircraft crew† | 2/7 | 1.1 | 0.1-7.1 | 2/7 | 1.1 | 0.1-7.1 |
| Railway transport workers, nec† | 3/8 | 1.8 | 0.3-9.1 | 3/7 | 2.1 | 0.3-11.8 |
| Ship transport workers, nec† | 4/12 | 1.4 | 0.3-5.3 | 4/12 | 1.4 | 0.3-5.3 |
| Shipbuilding workers, nec† | 0/5 | 0 | 0-6.0 | — | — | — |
| Transport engineers and firemen† | 1/6 | 1.0 | 0-13.7 | 1/6 | 1.0 | 0-13.7 |
| Stationary engineers, boilermakers† | 2/11 | 0.8 | 0.1-4.4 | 2/11 | 0.8 | 0.1-4.4 |
| Service station attendants and managers† | 4/19 | 0.8 | 0.2-2.8 | 4/15 | 1.0 | 0.2-3.7 |
| Vehicle mechanics† | 5/20 | 0.9 | 0.2-2.9 | 5/20 | 0.9 | 0.2-2.9 |
| Small equipment repairers† | 3/10 | 2.9 | 0.4-18.5 | 3/9 | 3.8 | 0.5-30.1 |
| Industrial mechanics† | 2/10 | 1.0 | 0.1-5.5 | 1/9 | 0.5 | 0-4.3 |

* Adjusted for sex, age (in 3 strata: < 60, 60-69, and ≥ 70 years), and cigarette smoking (in two strata: 0-19 and ≥ 20 pack-years).
† All exposed cases and controls were men.
— No cases, no further analyses done. nec = Not elsewhere classified.

female control were employed in garment making. Men in this group had varying jobs, none in garment making. Most of the cases mentioned exposure to fabric dust, and some remarked on the fabric finish, cleaning solvents, and sewing machine oil. None of the textile worker cases had been employed in other occupations found to be at risk in this study or considered beforehand to be at risk. Four of the cases and none of the controls were non-smokers.

Risk estimates ≥3.0 were measured in four other occupational groups in the ever employed analysis: pulp and paper mill workers; miners, drillers, and blasters; welders; and plumbers and pipefitters. All exposed cases and controls in these occupations were men. For all except the pulp and paper mill group, risks increased with ≥10 years of employment.

An examination of job duties among these occupational groups showed an interesting pattern related to pulp mill employment. Among the welders, one case had worked in pulp and paper mill construction. Many pulp mill piping systems are stainless steel, and welding this metal produces fumes containing nickel and hexavalent chromium.[19] Two other cases may have had similar exposures: a pulp mill pipefitter (included in both the plumber-pipefitter and pulp-paper mill worker occupational groups), and a pulp mill instrument fitter (in the pulp and paper mill group). The

remaining case who had worked at a pulp mill had no specific job details given, because the interviewee was a next of kin. All of the pulp and paper mill worker controls were involved in production rather than maintenance jobs, and none of the welder or plumber-pipefitter controls reported working in pulp and paper mills or other industries likely to involve stainless steel welding.

The cases in the miners, drillers, and blasters group had widely varying work descriptions, which did not suggest exposures in common. Two worked underground and four above ground.

Among occupational categories originally considered suspect, those involving work with wood or leather had ORs consistently <1.0: sawmill workers; forestry and logging workers; carpenters and woodworkers; and shoe and leather workers. Consistent with the results obtained in the analysis of these occupational groups, ORs were <1.0 for occupational exposures to the following agents and processes which have been strongly associated with nasal cancer in other studies: hardwood dust (OR 0.6, 95% CI 0.1 to 3.0); softwood dust (OR 0.7, 95% CI 0.3 to 1.6); furniture or cabinet making (OR 0.7, 95% CI 0.1 to 3.8); boot or shoe manufacture or repair (no cases); and leather tanning or processing (no cases). Chemical and biological laboratory personnel were also not at increased risk of nasal cancer.

Smelter and foundry workers, who might have been exposed to nickel or chromium, showed slightly increased risks only with a 20 year latency period taken into account. Painters had increased risks that increased with latency. Machinists also had raised risks that increased with both duration of exposure and latency. No pattern of duties or exposures was found within any of the occupational groups originally suspected of being at high risk.

The histologies of the nasal cancers in this study included 23 squamous cell carcinomas, seven melanomas, seven lymphomas, two adenocarcinomas, two adenoid cystic carcinomas, and seven other histologies with one case each. A histology specific analysis was judged possible only for squamous cell carcinoma (n=23). One control who was more than two years older than the remaining cases was excluded from the reanalysis (n=158). The following occupational groups had ORs ≥3.0 in the ever employed analysis: textile workers (OR 5.3, 95% CI 0.2 to 107); sheet metal workers (OR 5.3, 95% CI 0.1 to 470); machinists (OR 4.3, 95% CI 0.6 to 29.2); railway transport workers not elsewhere classified (OR 4.2, 95% CI 0.6 to 26.7); hairdressers and barbers (OR 4.1, 95% CI 0 to 502); and welders (OR 3.1, 95% CI 0 to 267). Only the railway workers and machinists had at least three cases, but no pattern of duties or exposures was found within these occupational groups. All of the occupational groups that had ORs >3.0 in the analysis of all histologies had decreased risks for those ever employed in this analysis, indicating that the risks were not specific to squamous cell carcinoma. All the remaining occupational groups originally suspected of being at high risk had ORs <1.0 in this analysis. There were no pulp and paper mill workers or painters with this histology.

Adjustment for nasal polyps and decongestant use did not change the results sufficiently to alter the interpretation of the occupational analyses.

### BLADDER CANCER

Table 3 shows the associations between occupation and bladder cancer. Plumbers and pipefitters had an infinite relative risk, based on only one case. Sheetmetal workers had an OR of 5.4. Two of the four sheetmetal worker cases (but not the control) had worked in aircraft assembly, a job which has been reported to have exposure to carcinogenic aromatic amines.[23]

Miners, drillers, and blasters had an OR of 4.5 in the ever employed analysis. The relative risk estimate increased with duration of employment (≥10 years, OR 8.1). All but one case in this occupational group were men. Twelve cases and four controls mined underground where diesel exhaust fumes and oil mist exposures are often high. The most commonly named types of mines were gold (six cases, three controls), nickel (four cases, one control), and coal (three cases, one control).

Strongly increased ORs were measured in two other occupational groups in the ever employed analyses: hairdressers and barbers; and gardeners. All three cases in the hairdressers and barbers group recalled applying hair dyes. The control, who was a barber, did not. Gardeners had increased risk with increased duration of employment (≥10 years, OR infinity). There was no pattern of duties or exposures in this occupational group.

Among occupations shown to have increased risks in other studies, several had increased ORs in the ever employed analysis: painters; laundry personnel; chemical and petroleum workers; machinists; and textile workers. Except for the chemical workers, all of these had increased risks with ≥ 10 years of exposure. Only laundry workers and machinists showed consistent patterns of duties or exposures. Three of the laundry worker cases worked in dry cleaning, versus one control. Five machinist cases and three controls worked in traditional machine shops, doing metal grinding, drilling, and lathe work. All reported using cutting oils.

There were also some occupational groups, considered potentially at risk based on evidence from other studies, which did not have increased ORs in the ever employed analysis: smelter and foundry workers; motor vehicle operators; cooks; vehicle mechanics; and shoe and leather workers.

Sex specific analyses did not show any important differences from the sex adjusted analyses.

The cases of bladder cancer had the following histologies: 55 transitional cell carcinomas; 43 papillary transitional cell carcinomas; four squamous cell carcinomas; one adenocarcinoma; one colloid carcinoma; and one carcinoma not otherwise specified. As the papillary,

*Table 3 Odds ratios* showing associations between occupational groups and cancer of the urinary bladder, all cases (n=105) and controls (n=139) included*

| | *Ever employed* | | | *Most recent 20 years removed* | | |
|---|---|---|---|---|---|---|
| | *Cases/controls n* | *Ever employed OR* | *95% CI* | *Cases/controls n* | *Ever employed OR* | *95% CI* |
| Occupational groups with OR ≥ 3.0: | | | | | | |
| Plumbers and pipefitters† | 1/0 | ∞ | 0.1-∞ | 1/0 | ∞ | 0.1-∞ |
| Sheet metal workers† | 4/1 | 5.4 | 0.5-283 | 4/1 | 5.4 | 0.5-283 |
| Miners, drillers, and blasters | 19/6 | 4.5 | 1.6-14.7 | 18/6 | 3.9 | 1.4-12.5 |
| Hairdressers, barbers | 3/1 | 3.2 | 0.2-176 | 2/1 | 2.6 | 0.1-159 |
| Gardeners | 6/3 | 3.7 | 0.7-25.0 | 5/3 | 2.7 | 0.5-19.8 |
| Occupational groups originally suspect: | | | | | | |
| Painters | 4/3 | 2.8 | 0.4-21.3 | 2/2 | 2.0 | 0.1-33.0 |
| Laundry personnel | 5/4 | 2.3 | 0.4-13.9 | 4/4 | 1.8 | 0.3-11.3 |
| Chemical and petroleum workers | 15/10 | 1.8 | 0.7-4.9 | 14/7 | 2.2 | 0.8-6.8 |
| Machinists† | 8/7 | 1.6 | 0.5-5.7 | 7/6 | 1.6 | 0.4-6.3 |
| Textile workers | 3/3 | 1.5 | 0.2-13.5 | 3/3 | 1.5 | 0.2-13.5 |
| Smelter and foundry workers† | 6/8 | 1.0 | 0.3-3.3 | 6/6 | 1.3 | 0.3-5.1 |
| Motor vehicle operators | 21/26 | 0.9 | 0.4-1.9 | 21/22 | 1.1 | 0.5-2.4 |
| Cooks | 7/12 | 0.8 | 0.2-2.3 | 5/9 | 0.7 | 0.2-2.7 |
| Vehicle mechanics† | 12/17 | 0.7 | 0.3-1.7 | 11/17 | 0.7 | 0.3-1.6 |
| Shoe and leather workers | 2/6 | 0.4 | 0-2.6 | 2/5 | 0.4 | 0-2.9 |
| Other occupational groups: | | | | | | |
| Administrators, managers | 22/23 | 1.3 | 0.6-2.7 | 14/16 | 1.0 | 0.4-2.4 |
| Travelling managers and salesmen | 19/32 | 0.7 | 0.3-1.5 | 14/25 | 0.7 | 0.3-1.4 |
| Accountants, book-keepers | 13/18 | 1.1 | 0.5-2.7 | 13/17 | 1.2 | 0.5-2.9 |
| Engineers, designers† | 4/5 | 1.3 | 0.3-6.6 | 3/3 | 1.6 | 0.2-12.5 |
| Teachers, librarians | 10/12 | 1.2 | 0.4-3.5 | 9/7 | 1.7 | 0.5-5.9 |
| Sales clerks | 28/38 | 1.0 | 0.5-1.9 | 24/31 | 1.0 | 0.5-2.0 |
| Office clerks and secretaries | 19/23 | 1.3 | 0.6-2.9 | 15/21 | 1.0 | 0.4-2.3 |
| Healthcare workers | 6/9 | 0.9 | 0.2-3.3 | 5/8 | 0.8 | 0.2-3.2 |
| Chemical and biological laboratory personnel | 6/8 | 1.1 | 0.3-3.9 | 5/7 | 0.9 | 0.2-3.6 |
| Radio operators† | 7/7 | 1.2 | 0.4-4.3 | 7/7 | 1.2 | 0.4-4.3 |
| Surveyors, prospectors, trappers† | 7/6 | 1.4 | 0.4-5.5 | 5/6 | 1.0 | 0.2-4.3 |
| Warehouse clerks and labourers | 26/31 | 0.9 | 0.5-1.9 | 22/24 | 1.0 | 0.5-2.2 |
| Delivery personnel, unmotorised | 16/33 | 0.6 | 0.3-1.1 | 15/31 | 0.5 | 0.2-1.1 |
| Firefighters† | 1/4 | 0.4 | 0-4.6 | 14/ | 0.4 | 0-4.6 |
| Guards, police† | 10/8 | 1.7 | 0.6-5.1 | 7/2 | 4.6 | 0.8-46.4 |
| Armed forces personnel, nec | 38/32 | 1.5 | 0.8-3.0 | 38/32 | 1.5 | 0.8-3.0 |
| Janitors | 6/11 | 0.8 | 0.2-2.6 | 3/8 | 0.5 | 0.1-2.5 |
| Housekeepers‡ | 6/11 | 1.0 | 0.1-6.5 | 4/10 | 0.4 | 0-2.9 |
| Handymen and apartment caretakers | 7/14 | 0.6 | 0.2-1.6 | 4/3 | 0.9 | 0.1-5.9 |
| Food service personnel | 17/24 | 1.0 | 0.4-2.2 | 14/19 | 1.0 | 0.4-2.4 |
| Food processors | 13/19 | 0.9 | 0.4-2.2 | 11/19 | 0.7 | 0.3-1.8 |
| Farmers and farm labourers | 39/37 | 1.7 | 0.9-3.1 | 39/36 | 1.7 | 0.9-3.2 |
| Fisherment† | 4/4 | 0.9 | 0.2-5.3 | 4/3 | 1.4 | 0.2-10.0 |
| Forestry and logging workers† | 15/12 | 1.6 | 0.6-4.0 | 14/11 | 1.7 | 0.4-4.5 |
| Sawmill workers† | 15/18 | 1.0 | 0.4-2.3 | 13/17 | 0.9 | 0.4-2.2 |
| Pulp and paper mill workers† | 2/2 | 1.5 | 0.1-22.6 | 2/2 | 1.5 | 0.1-22.6 |
| Welders† | 4/4 | 0.9 | 0.2-5.6 | 3/3 | 0.9 | 0.1-7.2 |
| Construction foremen† | 8/5 | 1.5 | 0.4-6.0 | 6/4 | 1.5 | 0.3-8.1 |
| Construction labourers | 15/21 | 0.8 | 0.3-1.7 | 14/17 | 0.9 | 0.3-2.1 |
| Bricklayers, plasterers, and cement workers† | 7/7 | 1.4 | 0.4-5.0 | 7/5 | 1.9 | 0.5-8.1 |
| Electricians and electrical equipment installers† | 2/9 | 0.3 | 0-1.6 | 2/7 | 0.4 | 0-2.0 |
| Carpenters and wood workers, nec† | 18/24 | 0.9 | 0.4-1.9 | 11/22 | 0.6 | 0.2-1.4 |
| Heavy equipment operators† | 9/7 | 1.3 | 0.4-4.5 | 7/7 | 1.0 | 0.3-3.6 |
| Pilots, aircraft crew† | 4/7 | 0.8 | 0.2-3.2 | 4/7 | 0.8 | 0.2-3.2 |
| Railway transport workers, nec† | 3/8 | 0.5 | 0.1-2.1 | 3/7 | 0.6 | 0.1-2.6 |
| Ship transport workers, nec† | 9/11 | 0.9 | 0.3-2.7 | 9/11 | 0.9 | 0.3-2.7 |
| Shipbuilding workers, nec† | 6/5 | 1.5 | 0.4-6.6 | 5/4 | 1.8 | 0.4-6.3 |
| Transport engineers and firemen† | 3/6 | 0.6 | 0.1-2.7 | 3/6 | 0.6 | 0.1-2.7 |
| Stationary engineers, boilermakers† | 6/11 | 0.7 | 0.2-2.1 | 6/11 | 0.7 | 0.2-2.1 |
| Service station attendants and managers† | 6/18 | 0.3 | 0.1-0.99 | 5/14 | 0.4 | 0.1-1.1 |
| Small equipment repairers† | 7/10 | 1.0 | 0.3-3.2 | 5/9 | 0.8 | 0.2-3.0 |
| Industrial mechanics† | 10/9 | 1.4 | 0.5-4.2 | 10/8 | 1.5 | 0.5-4.8 |

* Adjusted for sex, age (in 3 strata: < 60, 60-69, and ≥ 70 years), and cigarette smoking (in three strata: 0-9, 10-39, and ≥ 40 pack-years).
† All exposed cases and controls were men.
‡ All exposed cases and controls were women. nec = Not elsewhere classified.

transitional, and squamous cell carcinomas all arise from the transitional cell line, and made up 97% of the tumours, no separate analysis by histology was performed.

Additional adjustment for consumption of coffee, tea, and diet soft drinks, and a history of bladder infections, abdominal injuries, and chemotherapy did not change results sufficiently to alter the interpretation of the occupational analyses.

## Discussion

### NASAL CANCER

Increased risks have been measured in textile workers elsewhere.[24 28] The specific exposure of interest is not known, although fabric dust has been considered a possibility.[25] Certain fibres are made from plant materials (cotton, linen, rayon), and may produce exposures similar to furniture workers and cabinet makers. Another similarity is the potential for concurrent exposure to formaldehyde. This chemical is used in permanent press applications and is considered probably carcinogenic by IARC.[13] Sewing machine oils may also be a carcinogenic exposure.[12]

Among four cases who had worked in the pulp and paper industry, three were known to have been maintenance workers and were likely to have welded or brazed stainless steel. Exposures to nickel and hexavalent chromium are likely in these operations; these metals have

been consistently associated with increased risks of nasal cancer and are considered to be known carcinogens.[16] Cohort studies of pulp and paper mill workers in the United States and Finland have not found nasal cancers, although these cohorts and the expected number of cases of nasal cancer (based on population rates) were quite small.[29–31]

Although exposures to chromium, nickel, and formaldehyde were queried in the exposure section of the questionnaire, they were not recalled by the pulp and paper maintenance worker or the textile worker cases. This is likely to be because these agents are constituents of composite materials and therefore not known to employees who are exposed.[32]

Several other occupational groups identified in this study have had increased risks of nasal cancer reported in the scientific literature: miners, drillers, and blasters;[24 27 28] plumbers;[26 28] painters;[24 33] and machinists.[26 28]

We found no associations with occupations exposed to wood dust or wood, in contrast to reported results.[13] The woods used in this region are almost exclusively softwoods, which have been associated with increased risks of squamous cell carcinomas of the nose and nasal cavities in previous investigations.[13 34 35] Earlier studies conducted in British Columbia and nearby Washington State accrued cases from 1939 to 1977 and 1979 to 1987 respectively.[34 35] The different result found in this study may reflect evidence that more recent exposures are relatively low (means <1 mg/m$^3$) in the major wood industries of this region (construction carpentry and production of primary products from forests).[36 37]

No associations were found with other occupational groups originally suspected of being at high risk. Increased risks of nasal cancer have been found elsewhere among nickel refining workers[16]; however, the smelters and foundries in British Columbia are not involved in nickel refining or alloy production. Chemical and biological laboratory personnel may have exposures to formaldehyde.[13] Although the OR estimate for the occupational group was not increased, both laboratory workers with nasal cancer reported this exposure, whereas half the controls did not. Boot and shoe manufacture and repair have been classified by IARC[12] as carcinogenic to humans. The lack of association in this study may reflect the fact that shoe and leather work are not usual occupations in British Columbia; only one of the controls had this occupation in this province.

### BLADDER CANCER

Increased risks of bladder cancer among miners have been reported elsewhere.[8 38–43] Diesel equipment is commonly used in above ground and underground operations, as is drilling equipment with cutting oils (Tom Carter, British Columbia Ministry of Energy, Mines, and Petroleum Resources, personal communication, 8 August 1994). Diesel exhaust has been designated as probably carcinogenic by IARC, and mineral oils have been designated as known human carcinogens.[12–14]

Hairdressers and barbers have shown increased risks of bladder cancer in numerous studies.[8 38 39 42–47] The IARC recently classified the occupations, hairdresser and barber, as probably carcinogenic to humans.[15] The suspected carcinogenic exposures include hair dyes, as well as coal tar derivatives and oils.[15]

Laundry personnel have been shown to have increased risks in many epidemiological studies.[39 44 47 48] The chlorinated aliphatic hydrocarbons, including carbon tetrachloride and perchloroethylene, have been postulated as aetiological agents; carbon tetrachloride was classified as possibly carcinogenic and perchloroethylene as probably carcinogenic by IARC.[12 49]

Increased risks of bladder cancer among machinists have been reported elsewhere.[38 40–42 44 50] The carcinogenic exposures of machinists cutting and grinding metals may include polycyclic aromatic hydrocarbons in used mineral oils and aromatic amines in synthetic cutting oils.[12]

Occupational groups with increased relative risks, but without clear patterns of job duties or exposures in this study have also been reported previously in the epidemiological literature as being associated with bladder cancer: painters;[9 10 36 40–44 51] tailors and textile workers;[8 36 39–41 43 44 51–53] and chemical and petroleum workers.[8–10 36 37 39–44 50 52–54] Painters use various pigments, extenders, and solvents; this job has been classified as carcinogenic to humans by IARC,[55] largely based on stronger evidence for lung cancer than bladder cancer. Tailors and textile workers may also have exposure to pigments and dyes. Several occupations with exposures to inks, aromatic amines, polycyclic aromatic hydrocarbons, and coal tars were included in the occupational group chemical and petroleum workers: printers, hot tar roofers, rubber processors, coal workers, and oilfield manual workers.

Three other occupations with increased risk estimates in this study have had fewer reports of positive associations with bladder cancer. Increased risks have been detected among plumbers,[36 38 52] sheet metal workers,[36] and gardeners or nurserymen.[40–42]

Several occupations which were originally suspected of being at high risk had no association with bladder cancer in this study. Consistently increased risks of bladder cancer have been found for aluminum production; the process has been classified by IARC as carcinogenic to humans.[12] The group smelter and foundry workers included one case and three controls who had worked at an aluminum smelter. The lack of an association in this study may be related to the case definition (see limitations).

Motor vehicle operators have often had increased risks of bladder cancer reported, although relative risks have generally been low.[37 38 40 42 44 50 51 53 54 56] Our results are consistent with several other studies which have found no excess risk.[8 26 41 53] A possible explanation for the lack of association in this study may be the rural and wilderness settings for much western Canadian vehicle traffic, unlike the urban

settings which may predominate elsewhere. Most studies which have examined vehicle mechanics as an occupational category have found increased risks.[38 40–43 54 56] Our study had results similar to others which did not.[44 53]

Although cooks and kitchen workers have shown increased risks in some studies,[9 42 43] our results are consistent with those from several other recent studies which found no association.[41 44 45] Leather workers have shown increased risks of bladder cancer in many studies,[9 36 40 42 43 51 56] although several reports have shown no excess.[8 37 44] As for nasal cancer, the lack of association for shoe and leather workers may simply reflect the paucity of leather working occupations within British Columbia.

### LIMITATIONS

The main limitation of this study was its small size, resulting in imprecise OR estimates. Looking for patterns of duties or exposures among at least three cases in an occupational group, as well as increased relative risks, acted as a check for selecting occupations of interest for surveillance follow up.

Grouping of jobs meant that people with different work duties and exposures were included in the same occupational group, usually expected to result in non-differential misclassification and bias of risk estimates to the null.[57] This may have been a special issue for trades occupations the exposures of which would also be influenced by their industry of employment. As a check, we looked for patterns of exposure among occupations with increased ORs, and if they suggested an industry of interest, all the job listings for that industrial code were examined descriptively.

This study excluded carcinomas in situ. The natural history of many bladder cancers may include a prolonged period (years) of transitional cell carcinoma in situ before development of invasive carcinoma. Difficulty in classifying a tumour as invasive or in situ was responsible for most of the changes in histological eligibility of bladder cancer in this study. Some epidemiologists have recommended that in situ carcinomas be included in case definitions[10 51]; however, comparisons of occupational associations with invasive and in situ cancers in the United States national bladder cancer study indicated that risks were very similar.[58] Therefore exclusion of in situ tumours should not bias results, except when at risk occupational groups are screened to allow early detection. This may have been the case for aluminum smelter workers in British Columbia, who were made aware of their risk in a recent cohort study.[59]

### SURVEILLANCE FOLLOW UP

Results from these studies were used to select occupations which warranted follow up investigations in British Columbia work sites. Two occupational groups with increased risks of nasal cancer and three or more cases with similar duties or exposures were selected: textile workers (suspect exposures: formaldehyde, oils, fabric dust); and pulp and paper workers (suspect exposures: chromium and nickel from stainless steel welding or brazing in maintenance jobs). These jobs were held by 10 cases, representing 21% of the cases of nasal cancer. None had been recognised previously in compensation claims or penalty actions by the local regulatory agency despite evidence linking the job or its exposures to nasal cancer in the scientific literature.

Four occupations had increased risks of bladder cancer and showed shared patterns of job duties or exposures among three or more cases: mining (suspect exposures: diesel exhaust and oil mist); machining (suspect exposures: polycylic aromatic hydrocarbons and aromatic amines in cutting oils); hairdressing (suspect exposures: hair dyes as well as coal tar derivatives and oils); and drycleaning (suspect exposures: volatile chlorinated aliphatic hydrocarbons). These jobs were held by 33 cases, representing 31% of the cases of bladder cancer. Two of these occupations had not been previously recognised by the local regulatory agencies, in either penalty actions or compensation claims: hairdressers, and machinists.

The value of disease surveillance in this study will only be known after workplace follow up determines whether exposures to carcinogens continue in the targeted occupations. The responsible British Columbia regulatory agencies, as well as occupational hygienists in the pulp and paper industry have been informed of the study results to target exposure measurements and control strategies. Some of the targeted occupations are found in small shops which are unlikely to employ professional health and safety personnel. Without attention from regulatory agencies, exposures to carcinogens in these work sites are unlikely to be recognised.

We thank the following people for their assistance during the design, conduct, or analysis of this study: Jody Slakov, Dr Paul Demers, Ruth Hershler, Dr Clyde Hertzman, Bob Hirtle, Dr Steve Marion, Dr Anne Milner, and Hazel Sarginson. We are grateful to all the cases, controls, and next of kin who gave their time to take part in this study. The study was supported by the British Columbia Health Research Foundation.

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