Cancer Causes and Control **15**: 1007–1019, 2004.

A case–control study of occupational risk factors for bladder cancer in Canada

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Received 1 July 2003; accepted in revised form 7 July 2004

Key words: bladder neoplasms, case–control studies, human, occupational diseases.

Abstract

Objective: To investigate occupational risk factors for bladder cancer in seven Canadian provinces.
Methods: We analysed a population-based case–control dataset of 887 individuals with incident, histologically confirmed bladder cancer between 1994 and 1997. Controls (2847) frequency matched for age and gender were surveyed in 1996. Questionnaires were returned by about 60% of subjects. Odds ratios (ORs) for occupations and self-reported exposures were adjusted for province, age, race, smoking, and several dietary factors, using unconditional logistic regression.
Results: Statistically significant increased risks were observed among men employed as hairdressers (OR = 3.42; 1.09–10.8), primary metal workers (OR = 2.40; 1.29–4.50), miners (OR = 1.94; 1.18–3.17), and automechanics (OR = 1.69; 1.02–2.82). Primary metal workers and automechanics showed evidence of an employment duration–response trend. Modest elevated risks that were not significant were also observed for male government inspectors, printers, firefighters, general labourers, and welders. A duration–response trend was evident for government inspectors and general labourers. For females, significant elevations were observed among lumber processors (OR = 8.78; 1.28–60.1), general labourers (OR = 2.18; 1.05–4.52), nurses (OR = 1.54; 1.03–2.31), and general clerks (OR = 1.48; 1.01–2.17). The latter showed a positive duration–response trend.
Conclusions: This study found a statistically significant excess risk of bladder cancer, with a duration–response trend, among male primary metal workers and automechanics, and female office workers engaged in general clerical duties.

Introduction

Smoking tobacco is a major risk factor for bladder cancer and has been estimated to account for about 50% of bladder cancer cases [1]. Occupational factors also appear to have a substantial impact on bladder cancer incidence. It has been estimated that about 20–25% of male cases in the general population can be attributed to occupational exposures [2–5], although some estimates have been lower [6–8]. The evidence for a causal association is strong for dye workers, aromatic amine manufacturers, and rubber workers – occupations which likely involved exposure to one or more aromatic amines which are confirmed bladder carcinogens. The risks to more recent workers in these industries are likely to be

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lower due to legislative and industrial process changes, but this needs to be confirmed. There is also evidence of an increased risk in a variety of other occupations. Bladder cancer has been found to be elevated in aluminum smelter and other metal workers, leather workers, truck drivers, painters, hairdressers, dry cleaners, mechanics and machinists [9, 10]. In addition to smoking, a number of non-occupational factors have also been suggested to be associated with bladder cancer. These include: (1) genetic factors such as race, family history, and genetic polymorphisms; (2) dietary factors such as consumption of fruit and vegetables, coffee, meat and fat, and total fluid intake; (3) infections and inflammation of the bladder; and (4) treatment-related factors such as use of phenacetin-containing analgesics, cancer chemotherapy, and radiation therapy [11–16].

This study makes use of information collected in a collaborative project in Canada called the National Enhanced Cancer Surveillance System (NECSS). This project collected data on cases of various cancers and controls, with the intent of improving our knowledge of environmental factors in cancer development [17]. Detailed occupational information was also collected and is utilised in this report. The objective of the present analysis was to examine the association between bladder cancer and specific occupations, while adjusting for important confounders. Analysis of this large dataset with detailed information on occupations and personal factors is intended to contribute to our understanding of occupational risks for bladder cancer.

Methods

Subjects and data collection

Incident cases of histologically confirmed bladder cancer in adults aged 20–74 were identified through the provincial cancer registries in seven Canadian provinces (Newfoundland, Prince Edward Island, Nova Scotia, Manitoba, Alberta, Saskatchewan, and British Columbia). A random selection of population controls were included in the NECSS programme by frequency matching age and gender to all cancer cases. Random digit-dialling was used to recruit controls in Newfoundland and Alberta. All other provinces used a random sample from the provincial health insurance plan database. The latter method excluded military personnel and their families and indigenous people from the control group. As a result all subjects indicating an occupation in the military and all Native Indians were removed from this analysis.

After obtaining physician approval to contact patients, mailed questionnaires with telephone follow-up when necessary, were used to obtain information from cases and controls regarding socio-demographics, occupational history, smoking history, specific agent exposures, and dietary habits. Most cancer patients received the questionnaire between 2 and 5 months after diagnosis. Controls were surveyed over the 1996 calendar year while cases were recruited over the time period 1994–1997. Sixty-six percent of male bladder cancer cases and 72% of the female bladder cancer cases who received questionnaires completed and returned them. This represented 58% of the male cases ascertained and 61% of the female cases ascertained. The response rate for male controls was 59% and for female controls 65%. The analysis was conducted using 887 cases and 2847 controls. No information was available on reasons for non-response. Response rates in a similar study in a Canadian province that did not measure bladder cancer, showed higher responses among rural residents and older subjects [18].

Up to 12 occupations per person were recorded by the type of industry, business or service, the company name, the main job duties, and job title. These data were categorised into Standard Occupational Classification (SOC, 1980) codes [19]. Occupations used in the analysis were identified by using both the SOC code as well as reviewing the information provided on the questionnaire. This ensured that job descriptions that could be coded to more than one occupational classification were included in the occupational groups analysed here. This manual review also allowed for more precisely focused occupations than provided by SOC coding alone. Employment duration for occupations were calculated from the time periods reported by respondents for each occupational activity over their lifetime. Participants were also asked whether they had ever worked with a number of agents for more than one year at work. Information on years of agent exposure was also collected. This self-reported exposure information was analysed separately from information on occupations held for at least one year full-time equivalent.

The socio-demographic and lifestyle risk factors which where available in the dataset and tested as likely confounders included: age; gender; ethnic group; smoking history; coffee consumption; fruit consumption; vegetable consumption; and fried food consumption which was used to estimate the fat content of the diet. Two additional factors were also tested as possible confounders: province; and income adequacy. Two factors collected in NECSS that have occasionally been related to bladder cancer, but which were not available for this analysis, are consumption of chlorinated

drinking water and physical activity levels. Age was coded to 5-year groups, all dietary factors were coded into quartiles of serving quantity, except coffee consumption which was divided into three serving categories. Recent consumption (2 years ago) of fried food was adjusted by indications that there was a different level of intake 20 years ago. Those indicating a much lower or much greater fried food consumption in the past were moved down or up one quartile of servings/week, respectively, relative to more recent consumption. Ethnic derivation was divided into three groups based on international incidence rates in males [9]. The main racial group consisted of North American and Western Europeans with standardised incidence rates of about 15–30/100,000; the second group were people from countries with bladder cancer rates of about 6–15/100,000, including Eastern Europeans, Asians, South Americans and blacks; and the last group included east Indians and Filipinos which appear to have bladder cancer rates of 6/100,000 or less. Income adequacy was determined from household income adjusted for number of household members. When this information was missing, household income by itself was used, followed by estimations based on education and job title to categorise subjects into low, low-middle, high-middle and high income adequacy groups. Tobacco-years were calculated as the number of packs of 20 cigarettes smoked per day times the number of years smoked. Added to this was the amount of pipe-years, cigar-years and chewing tobacco plug-years, with each unit of these types of tobacco counting as two cigarettes. Current smokers and ex-smokers who quit more than 2 years ago were coded into separate tertiles of pack-years.

Statistical analyses

Unconditional multivariable logistic regression modelling was used to examine the association between each occupation or agent and bladder cancer in males and females separately, while controlling for potential confounders. Models of non-occupational factors were developed for each gender by testing variables for association with bladder cancer at $\alpha \leq 0.25$ using univariate analyses. For males, potential confounders eliminated at this step were fruit, vegetable, and income adequacy. Province and race were entered as nominal variables. Logit plots confirmed the rest could be entered as ordinal variables: age (11 categories of 5-year age groups); ex-smoking (tertiles of pack-years up to 2 years ago); smoking (tertiles of pack-years); coffee consumption (three groups); and fried food consumption (quartiles) (see Table 1 for the category measures). A similar analysis was conducted for females, but in this case fried food did not remain in the model, while fruit consumption (in quartiles) remained. For consistency in modelling between males and females, all confounders found to be important for either gender were used in models for both. These confounders were age, province, race, smoking, ex-smoking, and consumption of fruit, fried food, and coffee.

Testing the inclusion of interaction terms for confounders did not improve model fits nor change substantially the odds ratios. The odds ratios for ever *versus* never employed in each occupation was determined by entering each into the model one at a time, with control for province, race, age, ex-smoking, smoking, and consumption of coffee, fried food, and fruit in both males and females. The ORs were also adjusted for other employment in occupations identified in the introduction as previously associated with an elevated risk. The suspect occupations included printers (potentially exposed to dyes), rubber workers, metal workers, leather workers (dropped from the analysis because there where no cases for this occupation), truck drivers, painters, hairdressers, dry cleaners, mechanics and machinists. These nine occupations were entered into all regression models for males in which occupational risks were assessed. For females, only hairdressers, painters, truckers and printers where included in every model since the other five variables had too few subjects for a meaningful adjustment. When analysing subgroups of these occupations (for example foundry workers), the related occupation (metal workers) was removed from the model. All subgroups of larger occupational groups (indented in the tables) were entered together in the logistic regression model. Subjects with missing values for confounders were dropped from all models. All final models were highly significant, and model fit was good according to the Hosmer and Lemeshow goodness-of-fit test and regression diagnostics [20]. Self-reported exposure duration information and calculated duration of employment in each occupation was used to evaluate exposure-response. Odds ratios for approximate tertiles of duration (>1–5, >5–15, >15 years) were calculated using the logistic regression model. A test of trend was conducted by entering the data on exposure or employment duration into the model as a continuous variable. The *p*-value of the coefficients with slopes indicating increasing ORs for increasing duration were recorded to determine the fit to a monotonic positive trend.

Results

The ORs calculated for non-occupational factors, with adjustment for all other non-occupational factors, is

Table 1. Bladder cancer odds ratios of the unconditional logistic regression for non-occupational factors[a]

	Male (n = 1965)			Female (n = 1769)		
	Case (n = 535)	Control (n = 1430)	OR (95% CI)	Case (n = 352)	Control (n = 1417)	OR (95% CI)
Ethnic origin						
N. Am./W. Europe	432	1112	Reference	296	1187	Reference
E. Eur/Asia/Black/S. Am.	92	245	0.77 (0.58–1.04)	52	186	0.88 (0.61–1.28)
East Indian, Filipino	4	65	**0.17** (0.06–0.48)	1	36	0.26 (0.04–1.95)
Unknown	7	8	–	3	8	–
Smoking						
Never	67	388	Reference	99	693	Reference
Ex-smoker <20 tob-yrs	97	359	1.22 (0.85–1.75)	64	332	1.23 (0.87–1.75)
Ex-smoker 20 to >40 tob-yrs	97	187	**2.22** (1.51–3.28)	29	77	**2.12** (1.29–3.51)
Ex-smoker ≥40 tob-yrs	86	138	**2.77** (1.83–4.18)	9	21	**3.40** (1.42–8.13)
Smoker <20 tob-yrs	19	112	1.25 (0.71–2.22)	37	123	**3.02** (1.89–4.82)
Smoker 20 to <40 tob-yrs	57	110	**2.92** (1.92–4.45)	67	109	**4.62** (3.09–6.91)
Smoker ≥40 tob-yrs	112	136	**4.14** (2.84–6.04)	47	62	**5.44** (3.38–8.76)
Total fruit servings per week						
0–5	181	447	Reference	108	309	Reference
>5–9	118	298	1.09 (0.80–1.49)	68	280	0.70 (0.47–1.03)
>9–15	124	388	0.81 (0.60–1.10)	100	422	**0.69** (0.48–0.99)
>15	112	295	1.17 (0.84–1.64)	76	404	**0.55** (0.37–0.82)
Unknown	0	2	–	0	2	–
Fried foods servings per week						
<1	87	297	Reference	76	339	Reference
1–2	136	385	1.23 (0.88–1.72)	103	373	1.35 (0.94–1.94)
3–4	114	323	1.25 (0.88–1.77)	74	341	1.14 (0.77–1.69)
≥5	178	377	**1.60** (1.16–2.22)	96	356	1.26 (0.86–1.83)
Unknown	20	48	–	3	8	–
Coffee number of cups						
0–3 per month	63	288	Reference	63	324	Reference
1–7 per week	92	341	0.99 (0.67–1.46)	80	310	1.05 (0.70–1.58)
2 to >6 per day	375	771	1.30 (0.92–1.83)	205	757	0.74 (0.52–1.07)
Unknown	5	30	–	4	26	–
Total vegetables servings per week						
0 to <13	155	440	Reference	79	302	Reference
13 to <18	117	314	1.06 (0.78–1.46)	84	333	1.14 (0.77–1.69)
18 to <25	134	343	0.93 (0.69–1.27)	98	402	1.18 (0.80–1.75)
≥25	129	331	0.95 (0.69–1.32)	91	378	1.18 (0.79–1.78)
Unknown	0	2	–	0	2	–
Income adequacy						
Low income	115	319	Reference	93	351	Reference
Lower middle income	170	409	1.11 (0.81–1.52)	123	464	1.04 (0.74–1.47)
Upper middle income	141	426	1.02 (0.74–1.41)	98	424	1.09 (0.76–1.57)
High income	109	276	1.14 (0.80–1.61)	38	178	1.06 (0.66–1.68)

[a] Odds ratios adjusted for 5-year age group, province, and all other variables in this table.

presented in Table 1. Race categorised by low and lowest bladder cancer risk groups compared to the North American/Western European ethnic reference group showed the expected pattern of decreasing risks. The male East Indian/Filipino group showed a significantly lowered risk of 0.17 (0.06–0.48) compared to the reference group. Also as expected, smoking was a strong risk factor for bladder cancer and showed a cumulative exposure–response trend in both smokers and ex-smokers. A cumulative smoking history of 40 tobacco-years or more in current smokers produced an elevated risk of 4.14 (2.84–6.04) in males and 5.44 (3.38–8.76) in females, compared to non-smokers. Greater fruit consumption reduced bladder cancer risk in females, cutting the risk in about half (OR = 0.55; 0.37–0.82) for women eating more than 15 servings per

week compared to those eating less than five servings per week. Fruit consumption had little effect on male bladder cancer risk, while consumption of five or more servings of fried foods per week produced a statistically significant excess risk in men (OR = 1.60; 1.16–2.22) compared to those reporting less than one serving per week. In females, those with higher fried food consumption showed modest elevations in bladder cancer risk that were not statistically significant.

The unadjusted OR from the univariate model for consumption of two or more cups of coffee per day *versus* less than three cups per month was significantly elevated in both males (2.25; 1.65–3.00) and females (1.39; 1.02–1.90). After adjustment for all other non-occupational variables in the unconditional logistic regression model, the odds ratios were lowered and were no longer significant (Table 1). In males, high *versus* little or no coffee consumption gave an OR of 1.30 (0.92–1.83), while in females it was 0.74 (0.52–1.07). For both genders, this reduction was almost entirely due to adjustment for province and smoking, confirming some co-linearity between smoking and coffee drinking. Among the smaller group of non-smoking males (67 cases and 387 controls), those drinking two or more cups of coffee a day showed a similar OR of 1.31 (0.61–2.81) compared to the non-drinker reference group, after adjustment for all other non-occupational factors. There were no significant variations in bladder cancer odds ratios by various levels of income adequacy or vegetable consumption for either gender in either the univariate model or the fully adjusted model. These two factors were not included in models used for analysis of occupational factors.

The risks associated with employment in occupational categories are presented in Table 2. All ORs are adjusted for eight non-occupational factors as well as nine suspect occupations in males and four suspect occupations in females. Only results with at least one case or control, and adding up to at least five subjects with occupational exposure are presented throughout this report. Male hairdressers showed a significantly elevated risk of 3.42 (1.09–10.8), while females showed no elevation. This was one of the occupations previously suspected of being related to bladder cancer. Two other suspect occupations also showed significant elevations in men. Primary metal workers showed an OR of 2.40 (1.29–4.50). This elevation was found in manual labour occupations in steelwork and other metal heating occupations, but not foundry work. The more professional group of 'other Metalworkers' consisted of managers, researchers, engineers and some scrap metal workers, which showed a more than three-fold elevated risk that was not significant. The third suspect occupation with significantly elevated risk was mechanics, who showed an elevated OR of 1.66 (1.16–2.38) due to work on automobiles and heavier duty machines in aircraft, railway equipment and other industrial applications. The remaining suspect occupations of drycleaner, machinist, rubber worker, painter, trucker and printer did not show significantly elevated risks in men or women.

The adjusted OR for female nurses was found to be significantly elevated (1.54; 1.03–2.31), while a similar elevated risk was not significant among the smaller number of their male counterparts. In office workers, risks were highest for the subgroups engaged in filing and general clerical duties, with the OR for female general clerical workers significantly elevated (OR = 1.48; 1.01–2.17). In contrast, office workers in accounting showed lowered risks, significantly so among men (0.48; 0.24–0.96). Male workers in mining occupations showed an overall elevated OR of 1.94 (1.18–3.17), with three subgroups of miners – supervisors, drillers and hauler/machinists – all showing elevated odds ratios. Female sawmill/lumber processing workers showed an elevated risk of bladder cancer (OR = 8.78; 1.28–60.1) but the number of subjects were very small. Work as a general labourer resulted in elevated risks for both genders, being statistically significant in females (OR = 2.18; 1.05–4.52). Of the 126 comparisons made for occupation in both genders in this analysis, 6 significantly elevated or reduced risks would have been expected by chance at the 5% level of significance. One significantly reduced and 10 significantly elevated ORs were observed.

A number of occupational ORs were elevated but not statistically significant. Government workers showed an elevated risk that was borderline significant in men. This increase appeared to be concentrated among inspectors/investigators in men, and science/engineering professionals in women (although numbers were small). Modest elevations in ORs were noted for firefighters, cleaners, drycleaners, furnacemen, and welders. Male truck drivers and printers also showed non–significant elevations whereas their female counterparts showed decreased risks. Other elevated risks that were not statistically significant among females included house/hotel cleaners, woodworkers/carpenters, and electrical occupations including electricians.

Odds ratios were also calculated for self-reported exposure to a number of agents, with control for the same non-occupational confounders as in Table 2, but with no adjustment for any occupational factors (data not shown). Significantly elevated ORs were found for males indicating they were ever exposed to asbestos (OR = 1.42; 1.03–1.96), mineral/cutting/lubricating oil

Table 2. Bladder cancer odds ratios of the unconditional logistic regression for occupation[a]

Occupations	Males			Females		
	Cases/Controls	OR	95% CI	Cases/Controls	OR	95% CI
Government worker	42/70	1.48	0.96–2.28	17/60	1.37	0.75–2.49
Manager/elected	7/10	1.29	0.44–3.81	2/5	1.86	0.28–12.5
Inspect/investigate	27/42	1.65	0.95–2.87	5/23	1.02	0.35–2.94
Science/engineer	6/18	0.73	0.27–1.98	2/4	6.70	0.97–46.5
Administration	4/10	0.75	0.21–2.65	3/18	0.57	0.15–2.18
Manager	110/314	0.80	0.61–1.05	35/171	0.87	0.57–1.32
Accountant, auditor, economist, finance worker	18/58	0.97	0.53–1.77	8/57	0.54	0.24–1.19
Chemical worker	16/39	0.88	0.45–1.70	1/17	0.30	0.04–2.42
Architect, engineer, draughtsman	46/120	0.90	0.61–1.34	1/7	0.70	0.07–6.81
Religious	4/12	1.01	0.27–3.90		–	
Teacher	27/99	0.81	0.51–1.31	27/175	0.74	0.47–1.17
Health care	13/64	0.55	0.28–1.08	52/190	1.40	0.98–2.02
Nurse	7/12	1.76	0.60–5.15	41/139	1.54	1.03–2.31
Technician	3/24	0.27	0.06–1.22	9/43	0.98	0.45–2.16
Other: dental, physio, Vets, doctors	3/24	0.40	0.11–1.40	2/7	1.47	0.50–4.31
Artist, writer, entertainer	18/43	1.39	0.75–2.59	5/34	0.82	0.29–2.27
Office worker	110/271	1.09	0.82–1.44	174/757	0.81	0.62–1.05
Typing/reception	14/26	1.45	0.70–3.03	80/356	0.79	0.58–1.07
Filing	5/6	2.11	0.60–7.43	10/33	1.57	0.69–3.54
Accounting	11/64	0.48	0.24–0.96	53/254	0.70	0.49–1.01
Sales clerk	25/74	0.85	0.49–1.49	57/209	1.03	0.72–1.46
Other clerks	44/92	1.46	0.95–2.25	49/162	1.48	1.01–2.17
Sales worker	105/292	0.81	0.62–1.08	90/317	1.18	0.87–1.59
Gas station attendant	13/42	0.65	0.33–1.32	1/12	0.30	0.04–2.55
Firefighter	8/13	1.51	0.59–3.84		–	
Police, guard, detective	18/39	1.19	0.64–2.24	1/9	0.52	0.06–4.67
Food handler	42–143	0.85	0.57–1.28	74/263	1.05	0.76–1.46
Housekeeper, cleaner	32/81	1.24	0.77–2.00	41/153	1.16	0.77–1.76
House/hotel cleaner	4/7	1.42	0.32–6.35	12/36	1.51	0.72–3.17
Janitor	28/71	1.26	0.76–2.10	19/67	1.05	0.58–1.91
Hairdresser[b,c]	8/6	3.42	1.09–10.8	6/34	0.75	0.28–2.01
Drycleaner[b]	4/5	1.24	0.23–6.64		–	
Farmer	138/290	1.13	0.86–1.49	27/59	1.43	0.84–2.44
Fisherman, fish production worker	21/77	0.86	0.47–1.55	6/33	1.12	0.40–3.19
Logger, wood cutter	28/70	0.95	0.57–1.57	1/4	0.96	0.09–9.84
Petroleum refinery worker	21/42	1.10	0.60–2.01		–	
Miner	38/49	1.94	1.18–3.17		–	
Supervisor	4/2	3.57	0.56–22.9			
Driller	4/2	5.72	0.62–52.6			
Hauler/machinist	29/42	1.79	1.03–3.12			
Primary metal worker[b]	25/25	2.40	1.29–4.50		–	
Steelworker	9/12	1.25	0.42–3.73			
Heater	7/11	1.74	0.54–5.57			
Foundry	5/12	0.54	0.16–1.83			
Other metalworker	5/5	3.45	0.82–14.5			
All Furnaceman[d]	9/18	1.33	0.56–3.15		–	
Boilermaker	5/11	1.14	0.37–3.49			
Machinist[b]	16/37	0.73	0.37–1.43		–	
Welder	25/41	1.34	0.76–2.38		–	
Rubber worker[b]	3/10	0.96	0.23–4.08		–	
Mechanic[b]	71/108	1.66	1.16–2.38		–	
Auto	36/48	1.69	1.02–2.82			
Heavy duty	48/68	1.45	0.90–2.49			
Instrument	14/13	1.39	0.51–3.80			
Sawmill worker, lumber processor	30/57	1.13	0.67–1.91	4/2	8.78	1.28–60.1
Pulp and paper worker	20/45	1.21	0.66–2.20	2/4	1.18	0.18–7.97

Table 2. Continued

Occupations	Males			Females		
	Cases/Controls	OR	95% CI	Cases/Controls	OR	95% CI
Textile worker	4/13	0.56	0.15–2.15	11/46	0.86	0.42–1.75
Tailor, sewer	5/8	0.83	0.23–3.08	11/45	0.80	0.39–1.64
Painter[b,c]	12/35	0.74	0.36–1.53	3/11	1.08	0.27–4.37
Concrete worker	10/25	0.79	0.34–1.86		–	
Wood worker, carpenter	45/106	1.16	0.76–1.75	4/9	2.03	0.51–8.06
All electrical and electronic eq. and electric power workers	48/111	1.08	0.72–1.61	4/10	1.85	0.46–7.39
Electrician	21/53	1.15	0.64–2.06	3/2	4.70	0.53–41.5
Roofer	1/11	0.16	0.02–1.31		–	
Mason, bricklayer	4/13	0.77	0.21–2.91		–	
Plumber, pipefitter	13/30	0.86	0.41–1.81		–	
Railroad worker	26/57	0.94	0.56–1.58		–	
Vehicle driver	78/167	1.08	0.79–1.49	4/10	1.14	0.23–5.64
Bus/taxi	12/48	0.50	0.25–1.00		–	
Trucker[b,c]	68/133	1.23	0.88–1.75	1/4	0.58	0.06–5.97
Supervisors	4/6	2.15	0.37–12.5		–	
Packer, warehouse worker, material handler, dockworker	34/101	0.82	0.52–1.30	13/58	0.74	0.38–1.46
Printer[b,c]	7/12	1.64	0.56–4.75	1/14	0.32	0.04–2.65
General labourer, handyman, any industry	88/195	1.35	0.99–1.83	14/36	2.18	1.05–4.52

[a] OR = odds ratio for ever *versus* never employed in each occupation for more than 1 year, with adjustment for age, province, race, smoking, ex-smoking, and consumption of fruit, fried food, and coffee. These ORs were also adjusted for employment in nine suspect occupations in men and four in women.
[b] Suspect occupations included in the logistic regression model for males.
[c] Suspect occupations included in the logistic regression model for females.
[d] Not adjusted for primary metal work due to overlap.

(OR = 1.36; 1.04–1.77), and benzene (OR = 1.83; 1.12–2.99). Non-significant elevations were found among males reporting exposure to arsenic salts (OR = 1.81; 0.69–4.76), dyestuffs (OR = 1.59; 0.82–3.08), and welding (OR = 1.24; 0.96–1.61). No significant findings arose in females, with non-significant elevations in those reporting exposure to asbestos (OR = 1.82; 0.72–4.60) and coal tar/soot/pitch/creosote/asphalt (OR = 1.88; 0.63–5.57). Occupational information gathered about job title, duties and place of work was generally thought to be more reliable than expecting subjects to know whether they were exposed to agents such as benzene at work. For example, the information gathered for males engaged in welding occupations was compared to responses to the question 'have you ever worked with any of the following for more than one year' under the heading of welding? There were 66 subjects that appeared to be employed as welders for at least one year, whereas 428 indicated they 'worked with' welding for at least one year. It appears likely that many subjects are including bystander exposures in their reports of working with agents. This is likely to be useful information, but the possibility of exposure misclassification is expected to be high for self-reported exposure. Analysis of exposure–response trends for self-reported exposures showed no monotonically increasing odds ratios with increasing duration of any exposure and no significant trend of cancer risk with exposure years as a continuous variable. For the three exposures showing an overall significant elevation (asbestos, mineral/cutting/lubricating oil, and benzene), all showed the highest elevation and statistically significant OR only in the shortest exposure duration of 1–5 years.

Trends were also evaluated among men by employment duration in selected occupations showing elevated overall ORs (Table 3). Monotonically increasing risks with increasing employment durations were found among male government inspectors, automechanics, and general labourers. The *p*-value for trend using the actual years of employment as a continuous variable confirmed these positive trends. For example, the OR after 20 years of employment as an automechanic yields an OR of 2.2 (1.04^{20}). The use of the continuous employment duration variable also identified a positive trend among general mechanics and primary metal workers. Two significant duration–response trends where also identified among female government workers, and other clerks (Table 4). Female government

Table 3. Selected bladder cancer odds ratios of the unconditional logistic regression for duration of occupation in males

a priori Occupations	Duration of employment (years)			Trend *p*-value/ slope[b]
	>1–5	>5–15	>15	
Government worker				
Cases	9	14	19	
Controls	18	19	33	
OR	1.39	1.73	1.21	0.23/–
95% CI	0.58–3.36	0.82–3.65	0.65–2.25	
Goverment inspect/investigate				
Cases	8	10	9	
Controls	15	19	8	
OR	1.14	1.19	**3.37**	0.02/1.04
95% CI	0.44–2.97	0.53–2.69	1.23–9.24	
Nurse				
Cases	0	0	7	
Controls	0	4	8	
OR	–	–	2.62	0.16/–
95% CI			0.84–8.12	
Hairdresser				
Cases	1	4	3	
Controls	0	2	4	
OR	–	4.7	1.98	0.24/–
95% CI		0.79–27.9	0.4–9.7	
Other clerks				
Cases	17	9	18	
Controls	47	23	22	
OR	1.11	1.03	1.56	0.41/–
95% CI	0.758–2.09	0.56–3.00	0.84–3.44	
Firefighter				
Cases	3	1	4	
Controls	4	3	6	
OR	2.00	0.86	1.36	
95% CI	0.43–9.49	0.708–8.93	0.36–5.16	0.49/–
Housekeeper, cleaner				
Cases	15	10	7	
Controls	34	30	17	
OR	1.51	1.06	1.12	0.59/–
95% CI	0.74–3.01	0.47–2.39	0.43–2.86	
Miner				
Cases	23	9	6	
Controls	18	12	19	
OR	**3.84**	2.04	0.75	0.46/–
95% CI	1.88–7.87	0.78–5.3	0.28–2.03	
Primary metal worker				
Cases	11	7	6	
Controls	14	4	7	0.01/1.06
OR	1.58	4.9	2.9	
95% CI	0.66–3.75	1.2–19.0	0.87–9.97	
Welder				
Cases	6	2	16	
Controls	12	10	18	0.25/–
OR	1.45	0.61	1.66	
95% CI	0.50–4.19	0.12–2.98	0.78–3.48	
Mechanic				
Cases	20	19	32	
Controls	28	35	45	0.07/1.02
OR	1.67	1.33	1.78	
95% CI	0.88–3.19	0.70–2.51	1.06–2.99	
Auto mechanic				
Cases	15	9	12	
Controls	25	14	9	0.01/1.04
OR	1.37	1.93	2.48	
95% CI	0.66–2.83	0.76–4.88	0.97–6.34	
Truck driver				
Cases	19	16	33	
Controls	46	24	62	
OR	1.14	1.50	1.19	0.25/–
95% CI	0.63–2.04	0.73–3.10	0.74–1.91	
Printer				
Cases	2	1	4	
Controls	7	2	3	
OR	1.03	3.17	1.72	0.75/–
95% CI	0.19–5.58	0.26–38.6	0.33–9.02	
General labourer				
Cases	41	27	19	
Controls	104	52	38	0.02/1.02
OR	1.26	1.45	1.54	
95% CI	0.84–1.9	0.85–2.5	0.82–2.89	

[a] The *p*-values from the Wald chi-square for the fit of each coefficient in the model is presented for those occupations with positive slopes. When $p < 0.1$, the slope value for the coefficient (OR/year) is also presented.

workers only showed an elevated OR of 3.21 (1.17–8.85) after more than 15 years of employment.

Discussion

The main findings of this analysis of bladder cancer cases and controls in Canada were the elevated risk of bladder cancer observed among male hairdressers, miners, primary metal workers, and mechanics, and female nurses, general clerks, lumber processors, and general labourers. Results confirm the importance of smoking and some dietary factors in the aetiology of bladder cancer.

This study had a number of limitations. Due to the exploratory nature of the study, many comparisons were made, some of which likely arose by chance. Although caution is therefore warranted, there were more statistically significant positive findings than would be

Table 4. Selected bladder cancer odds ratios of the unconditional logistic regression for duration of occupation in females

Occupations	Duration of employment (years)			Trend *p*-value/ slope[a]
	>1–5	>5–15	>15	
Government worker				
Cases	5	4	8	
Controls	25	23	12	
OR	0.81	1.01	3.21	0.03/1.03
95% CI	0.30–2.23	0.32–3.22	1.17–8.85	
Health care				
Cases	15	18	19	
Controls	54	53	83	
OR	1.38	1.63	1.25	0.21/–
95% CI	0.73–2.60	0.90–2.94	0.71–2.21	
Nurse				
Cases	14	14	13	
Controls	36	35	68	
OR	1.76	2.18	1.10	0.44/–
95% CI	0.87– 3.56	1.10–4.30	0.57– 2.08	
Other clerks				
Cases	1	11	37	
Controls	12	42	108	
OR	0.56	1.64	1.41	0.06/1.01
95% CI	0.07–4.74	0.79–3.42	0.91–2.17	
Housekeeper, cleaner				
Cases	1	2	9	
Controls	3	9	25	
OR	1.66	1.42	1.51	0.13/–
95% CI	0.14–19.8	0.26–7.64	0.64–3.58	
General labourer, handyman, any industry				
Cases	10	2	2	
Controls	20	7	9	
OR	3.33	1.13	1.17	0.17/–
95% CI	1.32–8.38	0.20–6.49	0.22–6.36	

[a] The *p*-values from the Wald χ^2 for the fit of each coefficient in the model is presented for those occupations with positive slopes. When $p < 0.1$, the slope value for the coefficient (OR/year) is also presented.

expected by chance. Also, the investigation of duration–response trends provides a check on whether the elevation may be related to cumulative occupational exposures. No direct information on specific exposures in occupations, or their levels, were available. Such misclassification of exposure that is based only on an overall job class would attenuate estimated risks for particular activities. A limitation of all case–control studies is the potential for a recall bias in the cancer patients compared to controls. Such a bias is plausible when asking respondents to note whether they were ever exposed to carcinogenic agents such as asbestos or benzene. This is one reason why little emphasis was given to these measures. But less bias is anticipated when asking cases and controls to record a thorough occupational history. Also, the participation rate was rather low compared to more than a dozen other case–control studies of bladder cancer, although response rates were similar to several others [21–25]. The possibility exists that those not responding are systematically different from participants. We have no information on the reasons for refusal since our ethics committee did not allow further contact after a subject declined to participate. However, the response rate for cases was very similar to that for controls. The strong points of this study centred around the use of histologically confirmed incident bladder cancer cases, and the extensive information available on non-occupational factors that enabled control for several important confounders. This included cumulative exposure information on dietary and lifestyle factors. The study also benefited from detailed information on employment durations, for which an analysis of occupational duration–response trends could be made. Finally, in spite of the absence of data for several Canadian provinces, the study was large enough to provide risk estimates for many occupational groups.

Regarding non-occupational factors, the risks for the three race groups defined in this study followed the pattern expected [9]: compared to Caucasians in North American and Europe with the highest risk, those of Oriental, Spanish or Black extraction had lower risks, and the smaller group of those with East Indian, or Filipino origins had substantially lower risks. Dose-related elevated risks for bladder cancer among ex-smokers and smokers were found, as has been widely reported. The finding of a 2–3-fold overall increased risk among smokers, and a 4–5-fold risk in heavy smokers is consistent with previous findings [9, 26, 27]. Income adequacy did not appear to affect bladder cancer risk in this study either before or after control for smoking and other factors. Workers in lower social classes have been found to show higher rates of bladder cancer, likely due to differing smoking rates and occupational exposures [28]. Other investigations do not confirm this finding, suggesting there have been changes in exposures related to income or education [29]. The dietary factors of fruit or fried food consumption had an impact on bladder cancer risk, but varied with gender in this analysis. Higher fruit intake was associated with a gradient of lowered risks for females, but not males. A statistically significant increased risk for bladder cancer was found only among males with higher fried food consumption. A recent meta-analysis of dietary factors for bladder cancer confirms higher risks with low fruit and high fat consumption, although this analysis does not distinguish

between males and females [30]. The finding of a protective effect of fruit but not vegetables for bladder cancer is consistent with another meta-analysis [31]. Consumption of more than two cups of coffee per day compared to essentially non-drinkers resulted in a slight elevation in males but not females. This modest effect of coffee consumption is consistent with previous findings. A pooled analysis of non-smokers in Europe showed small increases in bladder cancer risk in moderate male coffee drinkers and decreased risk in moderate female drinkers [32]. On the other hand, either gender consuming 10 or more cups per day showed about a doubled risk. A meta-analysis concluded that coffee consumption increases urinary tract cancer risk by about 20% [33], which is similar to that found for males in the present study. Another review noted the inconsistent results between males and females, and the absence of a dose–response relation, suggesting the generally weak association seen may not be causal [34].

For occupational exposures, there was a significant three-fold increased risk among male hairdressers, and a modest elevation for self-reported dyestuff exposure in men. But there did not appear to be a duration–response trend with either measure. Female hairdressers showed a decreased risk. IARC concluded in 1993 that there was consistent evidence of an excess risk of bladder cancer among male hairdressers of about 60% [35]. Recent pooled case–control studies in Europe showed little increased risk of bladder cancer in male hairdressers [36], and a decreased risk among females [37]. A study of 10,298 male hairdressers in Nordic countries found an SIR of 147 (125–173), while 26,545 female hairdressers also showed a decreased risk (SIR = 89; 63–123) [38]. There is some evidence the increased risk of bladder cancer in men is not related to dye exposure, but may be related to a pomade called brilliantine used in the past for hair grooming in men. The risk from such exposures appears to be diminishing with time [39].

Primary metal workers showed a significantly elevated overall risk and a duration–response trend that was statistically significant. The increased risk appeared to be related to the manual labour involved in heating and forming metal in steelwork and furnace work. However, no elevation in risk was observed among foundry workers. This finding is not consistent with previous studies – a recent meta-analysis showed a small overall risk elevation of about 16% for bladder cancer among foundry workers [40]. The 'other metalworkers' category included plant managers, engineers, and sheet metal tinsmiths. This small group showed a more than tripled risk of bladder cancer that was not statistically significant. Previous findings on 77,288 male smelter and metal foundry workers in Nordic countries indicated a slight elevation (SIR = 1.09; 1.01–1.18) [38]. A pooled case–control study in Europe showed a similar overall result for male metal processors (OR = 1.14; 0.93–1.39), although subgroups such as metal casters, supervisors and those not elsewhere classified showed about a doubled risk [36].

Mechanics servicing automobiles, heavy duty equipment in railroad, aircraft, or construction industries, or mechanics and repairers of other smaller machines and instruments, all showed elevated risks for bladder cancer. Odds ratios were significantly elevated for general mechanics and automechanics. The trend analysis using a continuous duration variable showed significant positive trends for mechanics and automechanics, and the categorical trend analysis showed a monotonically increasing bladder cancer OR for increasing employment duration as an automechanic. This is a rather stronger effect than seen in other studies. Weak elevations for mechanics have been previously reported, for example the surveillance study of 353,757 Nordic male mechanics and iron/metalware workers showed a bladder cancer SIR of 1.09 (1.05–1.14) [38], a large case–control study in the US found a smoking-adjusted OR of 1.2 (1.0–1.4) based on 353 cases of bladder cancer in mechanics [2], and a pooled analysis in Europe showed an OR of 1.16 (0.90–1.50) for motor-vehicle mechanics after control for smoking status [36]. Mechanics are potentially exposed to exhaust fumes and lubricating oils, either of which may contribute to bladder cancer risk. One would anticipate a greater risk among heavy duty mechanics if diesel exhaust was causing the elevation, since this is more prevalent in trains and construction equipment than automobiles. Workers with self-reported exposure to mineral, cutting or lubricating oil showed significantly elevated odds ratios in the present analysis, but the highest risks were found in those exposed for shorter periods. According to the low ORs found for machinists in the present study, and the elevated ORs for mechanics, this would suggest that the elevated risk found for self-reported exposure to mineral, cutting or lubricating oil, is related more to the lubricating oils used by mechanics than the machining fluids commonly used by machinists. The literature on the association between machinist trades and bladder cancer is also not strong. Out of about 30 studies investigating the risk of bladder cancer among machinist trades, the largest high quality studies tended to show weakly elevated risks. The three largest case–control studies controlled for smoking in men and showed an OR of 1.16 (1.02–1.32) [36], 1.1 (1.0–1.3) [2], and 1.16 (0.95–1.41) [41]. A large surveillance study had no control for smoking but produced a similar estimate of 1.20 (1.11–1.29) in men [42]. Therefore, the reduced risks observed in this study are not consistent with other results on machinists.

Miners were also found to have a significantly elevated risk, but no evidence of a duration–response trend. The highest risk was found among miners employed for 1–5 years, who showed an OR of 3.84 (1.88–7.87). Those with more than 15 years of employment had a lowered risk. Although generally less dramatic for diseases such as cancer, the strenuous work required in this occupation may lead to a healthy survivor effect. This may account for some of the inverse trend. The overall elevation may be due to a number of exposures in these workers. For example, mining environments can have relatively high levels of diesel exhaust, which has been found in some studies to be related to a higher risk of bladder cancer, primarily in transportation workers [43]. While studies of miners have often shown decreased risks of bladder cancer [38, 44, 45], some of the larger case–control analyses have shown elevated risks among miners [2, 36, 46].

The occupations with statistically significant increased risk estimates were somewhat different among female workers, none of which were a priori suspect occupations. Both male and female nurses and general office clerks showed elevated risks, but only the results for females were statistically significant. This was due primarily to the higher number of females in these professions. No duration–response trends were apparent. It is difficult to suggest a cause of bladder cancer that has not already been controlled in this analysis for the general clerical occupations involved in filing, collecting payments, settling claims, arranging itineraries, providing tickets, registering guests, and so on. Nurses could conceivably have a greater opportunity for exposure to agents (such as chemotherapeutic drugs) that may affect bladder cancer incidence. A large excess risk was also identified for female sawmill workers that was statistically significant in spite of small numbers. No analogous increase was observed among male lumber processors. The doubled risk among female general labourers was statistically significant. This was consistent with a smaller elevation among the larger number of male general labourers. Two previous large case–control studies do not provide a complete report of results with which to compare these findings [47, 37]. In a survey of Nordic workers, about one half million female clerical workers showed an SIR of 1.15 (1.08–1.23), and about 83,000 female nurses had a bladder cancer SIR of 1.10 (0.94–1.29). These findings in females require further investigation and would benefit from fuller reporting of existing study results.

A number of suspect occupations showed some elevated ORs that were not statistically significant. Printers have an opportunity for dye and oil exposures, and indeed a non-significant elevated risk is seen for males which was higher in workers employed for more than 5 years. Females showed no elevation. Painters exposed to dyes and solvents on the other hand showed no increased risks in males and little increase in females. This was unexpected since there is consistent evidence in the literature that painters experience on average a 20–25% increased risk. Out of more than 50 studies considering painters, the 4 largest show significant elevations of 1.16 (1.06–1.26) [48], 1.39 (1.19–1.62) [38], 1.23 (1.05–1.43) [49], and 1.19 (1.00–1.41) [50]. Several large case–control studies that controlled for smoking also showed significantly elevated risks [2, 25], although there were some that showed no significant elevations [36, 41]. Truck drivers showed a slightly increased OR for bladder cancer that was not statistically significant, and no duration–response trend was identified. This modest increased risk is consistent with a recent meta-analysis of the literature which found an overall 17% increased risk among truck drivers [51]. In keeping with the lack of an effect among bus and taxi drivers found here, an earlier review found the evidence for an elevation in bus and taxi drivers to be less consistent and compelling than that for truck drivers [52]. There were few rubber workers in this study and these showed no elevated bladder cancer risk. Other studies have found high risks for rubber workers [53]. We could therefore neither confirm nor rule out an ongoing cancer risk among these rubber workers.

A number of occupations that were not initially suspected of contributing to bladder cancer also showed elevated ORs. Among males, government workers showed an increased risk. The most notable increase was found among long-term government inspectors, a group that also showed a significant duration–response trend. It is conceivable that this was due to various onsite exposures encountered during inspection duties. Male firefighters had a non-significant elevation of about 50%. Both diesel exhaust and fire smoke inhalation could contribute to this finding. This is consistent with other suggestive evidence of a 20–30% increase that was not statistically significant in cohort and surveillance studies [54–56], and adds to only three previous case–control studies which all showed low odds ratios [57–59]. A small elevation was also noted for welders, which is consistent with other findings [36, 38]. Female government workers showed an elevated risk, and particularly showed a high OR for a small number of scientists and engineers, as well as managers or elected officials. A significant risk trend was observed in females by duration of employment as a government worker, with employment of more than 15 years associated with a significantly tripled risk. Female construction workers employed as electricians and wood workers showed

elevated ORs that were not significant since they were based on small numbers of workers. A modest non-significant elevation was also observed among house cleaners. These occupations have generally not been implicated as a cause of bladder cancer [37, 38, 47]. Previous investigations of bladder cancer and occupation in women found elevations among metal machinists [37, 47]. There were too few such workers in this study to evaluate this association, but those women reporting cutting or lubricating oil exposure showed a reduced risk of bladder cancer. This report does not confirm previous findings of significant elevations among female tailors [37] or chemical workers [47], although the non-significant elevation found among farmers is consistent with findings in Europe [37].

In summary, the findings reported here suggest that males employed as hairdressers, miners, primary metal workers, and mechanics experience an elevated risk of bladder cancer. A common theme in these occupations appears to be exposures to a variety of combustion products and/or oils. Similar types of exposures may have contributed to modest, non-significant elevations in risk among government inspectors, firefighters, welders, truck drivers, printers, and general labourers. Other slight elevations among male general clerks, nurses and cleaners do not generally involve such exposures. Common exposures are also difficult to identify for female occupations showing an elevated risk of bladder cancer. Female nurses, general clerks, lumber processors, general labourers, and some government workers would likely have diverse exposures. Further research is required to identify occupational causes of bladder cancer, especially for female workers.

Acknowledgements

This research uses data collected through the National Enhanced Cancer Surveillance System, a collaboration of the Surveillance and Risk Assessment Division, Centre for Chronic Disease Prevention and Control, Population and Public Health Branch, Health Canada, and the Canadian Cancer Registries Epidemiology Research Group. Any opinions expressed in this paper are solely those of the authors and do not necessarily reflect the position, policies or views of the Workplace Safety and Insurance Board.

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