

Exhibit 237

Occupation and bladder cancer risk in a population-based case-control study in New Hampshire

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Abstract

Objective: To identify occupations with excess bladder cancer risk in New Hampshire, where bladder cancer mortality rates have been elevated for decades.

Methods: Lifetime occupational histories were obtained from interviews with 424 cases and 645 controls in a population-based case-control study. Unconditional logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CI) for each occupation, adjusted for age and smoking. Analyses by duration of employment were carried out and interactions with smoking were examined.

Results: Male tractor-trailer truck drivers had an elevated risk for bladder cancer (OR = 2.4, CI = 1.4–4.1), with a significant positive trend in risk with increasing duration of employment ($P_{\text{trend}} = 0.0003$). Male metal/plastic processing machine operators also had a significant excess (OR = 4.9, CI = 1.6–15.1), attributable mainly to molding/casting machine operators (OR = 16.6, CI = 2.1–131). Elevated risk was also observed for male fabricators, assemblers, and hand workers (OR = 1.8, CI = 1.0–3.4). Women in certain sales occupations (sales clerks, counter clerks, and cashiers) had a significant excess risk (OR = 2.2, CI = 1.3–3.9) and a significant trend with duration of employment ($P_{\text{trend}} = 0.016$), as did female health service workers (OR = 4.1, CI = 1.6–10.7; $P_{\text{trend}} = 0.014$). There was a positive interaction between smoking and employment as a health service worker ($p = 0.036$).

Conclusions: These findings are generally consistent with previous studies. Elevated risks for male molding/casting machine operators, female salesworkers, and female health service workers, especially those with a history of smoking, require further investigation.

Introduction

Over the past five decades, numerous studies of occupational causes of bladder cancer have identified a multitude of potentially high-risk occupations. Despite these efforts, there is strong evidence of an association for only a handful of occupational groups: dyestuffs workers and dye users, aromatic amine manufacturing workers, rubber workers, leather workers, painters,

truck drivers, and aluminum workers [1]. For other occupations, findings have typically been based on small numbers of exposed subjects and have been inconsistent across studies [2].

In a population-based case-control study in New Hampshire, we examined a variety of risk factors for bladder cancer including occupation, cigarette smoking, drinking water contamination, past medical conditions, life style factors, and family history of bladder cancer. This paper reports on the occupational data from this study, with two main objectives: first, to identify high-risk occupations in New Hampshire, where bladder cancer mortality rates have been elevated for decades [3]; and second, to re-examine occupations that have been

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found to be associated with bladder cancer in previous studies.

Materials and methods

Study population

New Hampshire residents, ages 25–74 years, diagnosed with primary bladder cancer from July 1, 1994 to June 30, 1998 were identified from the New Hampshire State Cancer Registry. To be eligible for the study, subjects were required to have a listed telephone number and speak English. Of the 618 potential participants, less than 2% ($n = 10$) of physicians denied patient contact, 10% ($n = 63$) were reported as deceased by a household member or physician, 12% ($n = 75$) declined participation, and 1% ($n = 8$) were too ill to take part; in less than 1% ($n = 3$) of the households, no one answered after 40 attempts distributed over days, evenings, and weekends. We interviewed a total of 459 bladder cancer cases.

For efficiency, we shared a control group with a study of non-melanoma skin cancer conducted covering a diagnostic period of July 1, 1993 to June 30, 1995 [4]. We selected additional controls for bladder cancer cases diagnosed between July 1, 1995 and June 30, 1997 frequency matched to these cases on age (25–34, 45–54, 55–64, 65–69, 70–74 years) and gender. All controls less than 65 years of age were selected using population lists obtained from the New Hampshire Department of Transportation. The file contains the names and addresses of those holding a valid driver's license for the State of New Hampshire. Controls 65 years of age and older were chosen from data files provided by the Centers for Medicare and Medicaid Services (CMS) of New Hampshire. Of the 990 potential participants, 2% ($n = 18$) were reported as deceased by a member of the household, 26% ($n = 261$) declined participation, 3% ($n = 29$) were mentally incompetent or too ill to take part; in 2% ($n = 17$) of the households, no one answered after 40 attempts. A total of 665 controls were interviewed.

This study was reviewed and approved for human subjects protections by all participating institutions.

Questionnaire data

Those who agreed to participate underwent a detailed in-person interview, usually at their home. Questions covered sociodemographic information, tobacco use, and medical history prior to the diagnosis date. Controls were randomly assigned a comparable reference date to the cases' diagnosis dates.

At least two weeks before the interview date, participants were mailed a personal residence and work history calendar. They were asked to complete information on street address of each residence and job title and place of work for each job held. The interviewer reviewed the forms at the time of the interview to ensure that they were complete and described in the level of detail needed for coding and analysis.

Occupational coding and statistical analysis

Each job reported in the occupational history was coded according to the Standard Occupational Classification Manual (SOC) scheme [5]. For each occupation, bladder cancer risk was estimated separately for men and women using unconditional logistic regression models. Odds ratios (ORs) and 95% confidence intervals (CI) were calculated using SAS statistical software. Only those jobs held after age 15 were considered in the analysis. For each occupation, those never employed in the occupation being evaluated after age 15 comprised the reference group. ORs were adjusted for age (<50 years of age, 50–59, 60–69, 70+) and smoking status (never smoked, former smoker of ≤ 20 cigarettes per day, former smoker of > 20 cig/day, current smoker of ≤ 20 cig/day, current smoker of > 20 cig/day). $p < 0.05$ was considered statistically significant.

We examined bladder cancer risk for every two-, three-, and four-digit SOC code. As a general rule, results are presented only for occupations held by 15 men or 15 women. All two-digit SOC codes meeting this criterion are included. For the three- and four-digit codes, we present results only for occupations with ORs that were either statistically significant or ≥ 2.0 or ≤ 0.5 . We also show results for additional occupations if they assist in the interpretation of positive findings. Analyses by duration of employment (never [referent], < 5 years, ≥ 5 years) were carried out on workers in occupations with increased risk (*i.e.*, ORs that were statistically significant or ≥ 2.0); tests of trend were performed using the median duration of employment among controls for each duration category. We examined interactions with smoking when we detected a statistically elevated OR associated with the main effect of an occupation.

We conducted a separate analysis of *a priori* suspect high-risk occupations. We reviewed the literature to identify occupations with at least a 30% elevated risk that was statistically significant in a previous study or at least a 70% excess risk (irrespective of statistical significance) in two or more studies. An industrial hygienist (PS) assigned one or more SOC codes to each of these occupations; multiple codes were used if the name was not specific enough to assign a single code.

Many jobs could not be coded, such as those defined by an industry (e.g., “rubber workers”) or exposure (e.g., “zinc-exposed jobs”), or by a vague job title (e.g., “professional specialist”). We limited this analysis to codeable *a priori* occupations held by at least ten men or ten women.

Results

A total of 424 out of 459 cases (92%) and 645 out of 665 controls (97%) had sufficient information to be included in the analysis. There was little age difference between cases and controls among men and women (Table 1). Cases were more likely than controls to have a history of cigarette smoking. The proportion of former smokers was similar in cases and controls, but for each gender the prevalence of current smokers was about twice as high among the cases.

Risk by SOC code

Men who worked as metal and plastic processing machine operators and tenders (SOC 754) had a five-fold, statistically significant risk of bladder cancer (Table 2). Most of these workers were molding and casting machine operators, for whom the relative risk was quite high (OR = 16.6, 95% confidence interval [CI]=2.1–131). Based on the short job descriptions provided by the study participants, an industrial hygienist (PS) assessed whether the molded or casted material was metal or plastic. For metal molders/casters, the relative risk was 12.9 (1.6–106) (nine cases, one control) (not shown). For plastic molders/casters, there were three cases and no controls. Thus, the excess risk appears to apply to molders and casters of both metal and plastic materials.

Bladder cancer risk was significantly elevated among male fabricators, assemblers, and hand workers (SOC 77) (OR = 1.8, CI = 1.0–3.4). Most of these men were assemblers (SOC 772); the remainder were welders/solderers (SOC 771) or hand workers (SOC 775).

Men who drove tractor-trailer trucks (SOC 8212) had significantly increased bladder cancer risk (OR = 2.4, CI = 1.4–4.1). There was a 30% excess among men who drove light trucks (SOC 8214), but this was not statistically significant, and there was no excess for bus drivers (SOC 8215) or taxicab drivers (SOC 8216).

Two occupations were associated with significantly reduced risk among men: miscellaneous administrative support occupations, including clerical (SOC 479), and police/detectives (SOC 513). ORs of 0.5 or lower were found for industrial engineers (SOC 1634), real estate sales occupations (SOC 4123), financial record processing occupations (SOC 471), miscellaneous mechanics and repairers (SOC 617), miscellaneous textile machine operators (SOC 7659), and helpers (other construction trades) (SOC 8648), but none of these was statistically significant.

Women employed in marketing and sales occupations had elevated risk for every major sales category examined (SOC 40, 41, 42, 43). Retail sales occupations (SOC 43), the most common marketing/sales occupation in our study, had a 60% excess that was marginally significant. Retail sales occupations are composed of two broad categories of salespersons: those who sell specific commodities (SOC 434-5) and “other” retail salespersons (SOC 436). Risk was not elevated among salespersons of specific commodities (e.g., garments, shoes, jewelry) (OR = 0.7, CI = 0.3–1.7), but there was a significant excess among “other” retail salespersons (OR = 2.4, CI = 1.2–4.6). Most of these women were sales clerks (SOC 4362) or cashiers (SOC 4364), each of which had ORs above two; the remainder were counter

Table 1. Distribution of bladder cancer cases and controls by age and smoking status

	Men (n = 738)		Women (n = 331)	
	Cases n (%)	Controls n (%)	Cases n (%)	Controls n (%)
Age (years)				
25–39	5 (1.5)	10 (2.5)	5 (5.4)	21 (8.8)
40–49	24 (7.3)	37 (9.1)	10 (10.8)	38 (16.0)
50–59	70 (21.2)	70 (17.2)	25 (26.9)	49 (20.6)
60–69	136 (41.1)	184 (45.2)	29 (31.2)	81 (34.0)
70+	96 (29.0)	106 (26.0)	24 (25.8)	49 (20.6)
Smoking status				
Never	53 (16.0)	102 (25.1)	23 (24.7)	100 (42.0)
Former ≤ 20 cigarettes/day	33 (10.0)	66 (16.2)	11 (11.8)	53 (22.3)
Former > 20 cigarettes/day	145 (43.8)	171 (42.0)	21 (22.6)	38 (16.0)
Current ≤ 20 cigarettes/day	14 (4.2)	18 (4.4)	10 (10.8)	21 (8.8)
Current > 20 cigarettes/day	86 (26.0)	50 (12.3)	28 (30.1)	26 (10.9)

Table 2. Number of cases and controls and ORs by gender and occupation^{a,b}

SOC	Job title	Men				Women			
		Cases ^c	Cont ^c	OR	95% CI	Cases ^c	Cont ^c	OR	95% CI
11	Officials and administrators, public administration	11	18	0.8	0.4–1.7	3	8	0.9	0.2–3.8
12–13	Officials and administrators, other	111	130	1.1	0.8–1.5	12	41	0.8	0.4–1.6
14	Management related occupations	42	50	1.1	0.7–1.7	7	30	0.5	0.2–1.3
	149 Management related occupations, NEC	10	14	1.1	0.5–2.5	2	15	0.3	0.1–1.5
16	Engineers, surveyors, and architects	32	61	0.7	0.4–1.0	0	3	–	–
	1634 Industrial engineers	8	22	0.5	0.2–1.1	0	2	–	–
17	Computer, mathematical, and operations research occupations	7	15	0.7	0.3–1.8	1	4	1.4	0.1–12.8
18	Natural scientists	7	13	0.7	0.3–1.7	0	0	–	–
20	Social, recreation, and religious workers	11	22	0.7	0.3–1.4	7	21	0.8	0.3–2.0
22	Teachers: college, university, other postsecondary institution	5	11	0.7	0.2–2.0	2	9	0.6	0.1–3.2
23	Teachers, except postsecondary institution	11	25	0.6	0.3–1.2	12	37	0.9	0.4–1.9
29	Registered nurses	0	1	–	–	4	18	0.5	0.2–1.6
32	Writers, artists, performers, and related workers	15	14	1.4	0.6–3.0	3	9	0.9	0.2–3.4
36	Health technologists/technicians	2	6	0.5	0.1–2.7	2	14	0.4	0.1–1.7
37	Engineering and related technologists and technicians	15	29	0.6	0.3–1.2	0	4	–	–
38	Science technologists and technicians	10	9	1.4	0.6–3.6	2	5	0.9	0.2–5.2
39	Technicians; except health, engineering, and science	8	18	0.6	0.3–1.4	0	4	–	–
40	Supervisors; marketing and sales occupations	22	21	1.2	0.6–2.2	4	7	1.9	0.5–7.1
41	Insurance, securities, real estate, and business service sales occupations	26	35	0.9	0.5–1.5	5	8	1.6	0.5–5.7
	4123 Real estate sales occupations	5	16	0.5	0.2–1.3	2	1	5.9	0.5–76.2
42	Sales occupations, commodities except retail	31	37	1.1	0.6–1.8	3	6	1.6	0.4–7.5
43	Sales occupations, retail	69	80	1.2	0.8–1.7	39	77	1.6	1.0–2.8
	4359 Salespersons, NEC	9	12	0.9	0.4–2.3	2	14	0.4	0.1–1.9
	434–435 Salespersons, commodities	29	33	1.2	0.7–2.0	8	27	0.7	0.3–1.7
	436 Sales occupations, other	46	53	1.2	0.8–1.8	33	53	2.2	1.3–3.9
	4362 Sales clerks	17	28	0.8	0.4–1.5	22	32	2.4	1.2–4.6
	4363 Counter clerks	7	7	1.3	0.4–3.9	3	7	1.3	0.3–5.6
	4364 Cashiers	4	6	0.9	0.3–3.4	12	16	2.2	1.0–5.3
45	Supervisors; administrative support occupations, including clerical	10	11	1.2	0.5–2.9	1	2	0.7	0.1–8.8
46-47	Administrative support occupations, including clerical	67	88	0.9	0.6–1.3	44	125	1.0	0.6–1.6
	471 Financial record processing occupations	6	16	0.4	0.2–1.1	8	34	0.6	0.2–1.3
	479 Miscellaneous administrative support occupations, including clerical	2	13	0.2	0.04–0.9	11	29	1.2	0.6–2.7
50	Private household occupations	3	0	–	–	8	19	1.0	0.4–2.6
51	Protective service occupations	21	35	0.7	0.4–1.2	1	7	0.5	0.1–3.9
	513 Police/detectives	4	17	0.3	0.1–0.9	0	2	–	–
	5132 Police and detectives, public service	4	12	0.4	0.1–1.4	0	1	–	–
52	Service occupations, except private household and protective	77	81	1.2	0.9–1.8	44	101	1.3	0.8–2.2
	5217 Kitchen workers, food preparation	10	7	1.6	0.6–4.3	10	10	2.5	1.0–6.7
	523 Health service occupations	3	5	0.5	0.1–2.1	13	9	4.1	1.6–10.7
	5236 Nursing aides, orderlies, and attendants	2	1	1.4	0.1–16.9	9	7	3.3	1.1–10.0
55	Farm operators and managers	9	11	0.9	0.4–2.2	1	1	1.8	0.1–40.7
56	Other agricultural and related occupations	67	80	1.1	0.8–1.6	4	8	1.4	0.4–5.0
57	Forestry and logging occupations	17	25	0.7	0.4–1.3	0	0	–	–
60	Supervisors; mechanics and repairers	11	13	1.0	0.4–2.2	0	0	–	–
61	Mechanics and repairers	56	67	1.0	0.7–1.5	2	3	1.3	0.2–8.4
	617 Miscellaneous mechanics and repairers	5	13	0.4	0.2–1.3	0	2	–	–
64	Construction trades	76	100	0.9	0.6–1.3	1	4	1.2	0.1–11.9
68	Precision production occupations	55	74	0.8	0.6–1.2	9	15	1.4	0.6–3.5
71	Supervisors; production occupations	15	30	0.6	0.3–1.2	0	4	–	–
75	Machine operators and tenders (metals, plastics)	27	21	1.4	0.8–2.7	1	9	0.3	0.04–2.5
	754 Metal/plastic processing machine operators/tenders	15	4	4.9	1.6–15.1	0	3	–	–
	7542 Molding and casting machine operators/tenders	12	1	16.6	2.1–131.3	0	3	–	–
76	Machine operators and tenders (other)	80	93	1.0	0.7–1.4	24	48	1.1	0.6–2.0
	7659 Misc. textile machine operators	5	12	0.4	0.1–1.2	3	3	2.3	0.4–12.8

Table 2. (Continued)

SOC	Job title	Men				Women			
		Cases ^c	Cont ^c	OR	95% CI	Cases ^c	Cont ^c	OR	95% CI
77	Fabricators, assemblers, and hand working occupations	28	20	1.8	1.0–3.4	13	25	1.2	0.6–2.6
	771 Welders/solderers	6	5	1.3	0.4–4.5	1	5	0.3	0.04–3.1
	772 Assemblers	17	13	1.8	0.9–3.9	10	19	1.3	0.6–3.1
	775 Hand working occupations	4	2	2.8	0.5–16.0	2	5	1.0	0.2–5.6
78	Production inspectors, testers, samplers, and weighers	17	22	1.0	0.5–2.0	4	15	0.8	0.2–2.6
82	Transportation occupations	78	79	1.2	0.8–1.7	2	6	0.9	0.2–4.8
	8212 Truck drivers, tractor-trailer	47	25	2.4	1.4–4.1	0	0	–	–
	8213 Truck drivers, heavy	3	4	0.8	0.2–3.5	0	0	–	–
	8214 Truck drivers, light (including delivery and route drivers)	27	25	1.3	0.7–2.3	2	0	–	–
	8215 Bus drivers	5	10	0.5	0.2–1.6	0	5	–	–
	8216 Taxicab drivers and chauffeurs	8	10	0.8	0.3–2.3	0	1	–	–
83	Material moving occupations, except transportation	10	15	0.8	0.4–1.9	0	0	–	–
86	Helpers	26	35	0.9	0.5–1.5	1	2	1.7	0.2–21.1
	8648 Helpers, other construction trades	7	17	0.5	0.2–1.2	0	0	–	–
87	Handlers, equipment cleaners, laborers	103	114	1.1	0.8–1.5	4	18	0.5	0.1–1.4
91	Military occupations	235	283	1.0	0.7–1.4	6	12	1.1	0.4–3.1
99	Miscellaneous occupations	106	134	1.0	0.7–1.4	76	181	1.3	0.7–2.5

^a Adjusted for age and smoking.

^b Table includes all 2-digit SOC codes held by 15 men or 15 women. Table includes 3- and 4-digit codes held by 15 men or 15 women if the OR was statistically significant or ≥ 2.0 or ≤ 0.5 . Results for other selected occupations are included to facilitate interpretation of the results.

^c Number of people ever employed in each SOC code.

–: OR was not estimated because the occupation was held by 0 cases and/or 0 controls.

clerks, who had a 30% excess which was not statistically significant.

Female kitchen workers (food preparation) (SOC 5217) had an excess risk which was of borderline significance (OR = 2.5, CI = 1.0–6.7). Risk was elevated among women in two related occupations (not shown): food and beverage preparation/service supervisors (OR = 1.7, CI = 0.4–7.6, 4 cases, 4 controls) and cooks (other than short order) (OR = 2.0, CI = 0.4–8.8, 4 cases, 4 controls). Men employed in these occupations also had nonsignificant excesses: OR = 1.6, CI = 0.6–4.3 (10 cases, 7 controls) for kitchen workers (food preparation); OR = 3.6, CI = 0.7–18.1 (6 cases, 2 controls) for food and beverage preparation/service supervisors; OR = 1.3, CI = 0.5–3.6 (8 cases, 8 controls) for cooks (except short order); and short order cooks (3 cases, 0 controls).

Women employed in health service occupations (SOC 523) had a significantly increased risk of bladder cancer (OR = 4.1, CI = 1.6–10.7). Most of these women had worked as nurses' aides (SOC 5236) in hospitals and nursing homes, for whom an excess risk was also observed; the remainder were either dental assistants or health aides. There was no excess risk among registered nurses (SOC 29).

Several occupations held by women had relative risks of 0.5 or less, but the associations were not statistically significant, including management related occupations,

NEC (SOC 149); health technologists/technicians (SOC 36); salespersons, NEC (SOC 4359) and handlers, equipment cleaners, laborers (SOC 87).

For occupations associated with increased risk, we further estimated risks according to duration of employment (Table 3). Among male tractor-trailer drivers, there was a positive trend of increasing risk with duration of employment ($P_{\text{trend}} = 0.0003$), with a four-fold risk for men who held this occupation for five years or longer. Although a marginally significant trend was observed for metal/plastic processing machine operators/tenders ($P_{\text{trend}} = 0.065$), men who held this job for fewer than five years had a higher bladder cancer risk than those who worked for five years or longer; this is likely attributable to small numbers of workers with five or more years of employment.

Among women, significant positive trends in risk with increasing duration of employment were observed for "other" retail sales occupations ($P_{\text{trend}} = 0.016$); long duration (≥ 5 years) was associated with increased risk for both sales clerks ($P_{\text{trend}} = 0.019$) and cashiers ($P_{\text{trend}} = 0.061$). There was a significant trend in risk with duration of employment in health service occupations ($P_{\text{trend}} = 0.014$), with an OR of 5.8 (CI = 1.3–26.8) for women who held this occupation for at least five years.

We assessed whether a history of cigarette smoking modified the risks we detected for specific occupations.

Table 3. Bladder cancer risk according to duration of employment in selected SOC codes^{a,b}

	Duration (yr)	Cases ^c (n)	Controls ^c (n)	OR	95% CI	Trend test (P)
Men						
754 Metal/plastic processing machine operators/tenders	<5	12	2	7.3	1.6–33.6	0.065
	≥5	3	2	2.3	0.4–14.5	
77 Fabricators, assemblers, and hand working occupations	<5	15	11	1.9	0.8–4.3	0.178
	≥5	13	9	1.8	0.7–4.3	
8212 Truck drivers, tractor-trailer	<5	19	16	1.5	0.8–3.1	0.0003
	≥5	28	9	4.0	1.8–8.7	
Women						
436 Retail sales occupations, other	<5	21	36	2.0	1.0–4.0	0.016
	≥5	12	17	2.6	1.1–5.9	
4362 Sales clerks	<5	15	25	2.1	1.0–4.5	0.019
	≥5	7	7	3.2	1.0–9.9	
4364 Cashiers	<5	6	8	1.8	0.5–6.0	0.061
	≥5	6	8	2.8	0.9–8.7	
5217 Kitchen workers, food preparation	<5	8	9	2.3	0.8–6.7	0.121
	≥5	2	1	4.1	0.4–47.6	
523 Health service occupations	<5	7	6	3.3	1.0–10.8	0.014
	≥5	6	3	5.8	1.3–26.8	
5236 Nursing aides, orderlies, and attendants	<5	5	5	2.9	0.8–11.2	0.057
	≥5	4	2	4.3	0.7–28.0	

^a Adjusted for age and smoking.

^b Table includes only SOC codes held by 15 men or 15 women, with an association that was statistically significant or ≥2.0 in Table 2.

^c Number of men or women employed in each occupation for the specified duration.

We found a positive interaction between occupation and smoking for female health service workers (SOC 523) ($p=0.036$) (Table 4); women in this occupation who had ever smoked had a 20-fold risk of bladder cancer. The joint effects of smoking and several other occupations (male fabricators, assemblers, and hand workers; male truck drivers; female “other” retail sales occupations; and female sales clerks) were somewhat stronger than an additive model would yield, but were not statistically significant.

Risk for “a priori” occupations

A priori occupations with ORs of 1.3 or higher, other than those discussed above, are shown in Table 5; those with weaker associations are listed in Appendix A. *A priori* occupations that do not appear in either table were held by fewer than ten men and ten women in our study population.

Our study was consistent with previous reports of elevated bladder cancer risk among male garage and/or

gas station workers, gardeners, plumbers, and woodworkers, and female hairdressers. However, none of the associations was statistically significant and there were no significant trends with duration of employment.

Discussion

This study is the first population-based case-control study of occupational bladder cancer incidence in New Hampshire. We found significantly elevated bladder cancer risk among male tractor-trailer drivers; metal and plastic molding and casting machine operators; fabricators, assemblers, and hand workers; and among female sales workers and health service workers. Our findings also support an excess risk among garage and gas station workers, gardeners, plumbers, woodworkers, and hairdressers.

An excess bladder cancer risk among male truck drivers has been well documented [6–13], including in a bladder cancer mortality study conducted in New

Occupation and bladder cancer

Table 4. Interactions between smoking and employment in selected occupations^{a,b}

Men		SOC 754: Metal/plastic processing machine operators/tenders		SOC 77: Fabricators, assemblers, and hand working occupations		SOC 8212: Truck drivers, tractor-trailer	
Ever Smoked	Ever Held Job	n (cases/controls)	OR (95% CI)	n (cases/controls)	OR (95% CI)	n (cases/controls)	OR (95% CI)
No	No	52/102	1.0	49/97	1.0	49/99	1.0
Yes	No	264/301	1.7 (1.2–2.5)	254/290	1.7 (1.2–2.5)	235/283	1.7 (1.1–2.4)
No	Yes	1/0	–	4/5	1.7 (0.4–6.6)	4/3	2.6 (0.6–12.0)
Yes	Yes	14/4	7.2 (2.2–23.0)	24/15	3.1 (1.5–6.6)	43/22	3.9 (2.1–7.3)

Women		SOC 436: Retail sales occupations, other		SOC 4362: Sales clerks		SOC 523: Health service occupations		SOC 5236: Nursing aides, orderlies, and attendants	
Ever Smoked	Ever Held Job	n (cases/controls)	OR (95% CI)	n (cases/controls)	OR (95% CI)	n (cases/controls)	OR (95% CI)	n (cases/controls)	OR (95% CI)
No	No	14/79	1.0	17/87	1.0	22/94	1.0	22/95	1.0
Yes	No	46/106	2.3 (1.2–4.5)	54/119	2.2 (1.2–4.1)	58/135	1.8 (1.0–3.1)	62/136	1.9 (1.1–3.3)
No	Yes	9/21	2.6 (1.0–6.9)	6/13	2.4 (0.8–7.3)	1/6	0.7 (0.1–6.4)	1/5	0.9 (0.1–8.1)
Yes	Yes	24/32	4.7 (2.1–10.3)	16/19	4.6 (2.0–10.9)	12/3	19.7 (4.9–78.9)*	8/2	19.3 (3.7–100.5)

^a Adjusted for age.

^b Table includes only those occupations with significantly elevated risk in Table 2.

* Interaction term: $p = 0.036$

England [6, 10]. Some investigators have attributed this to diesel exposure. In one study, there was a consistent gradient of bladder cancer risk with increasing duration of employment for men who drove trucks after 1950, when diesel became a common fuel, but not for those who drove only prior to 1950 [11]. However, in another study risk was greater in men who began driving trucks in the 1930s and 1940s [6]. In both studies, risk was higher for truck drivers reporting diesel exposure than for those who did not, but non-diesel truck drivers were also at increased risk, suggesting that a factor other than diesel was partially responsible. Exposure to motor exhaust in general has also been offered as an explanation for the elevated bladder cancer risk among truck drivers [2, 6, 11, 12]; this is supported by observations of excess risk among taxicab and bus drivers [2, 12]. Researchers have also speculated that the bladder cancer excess among truck drivers could be related to factors such as urinary retention and exposure to concentrated cigarette smoke inside the truck cab [6, 12], but these factors have not been evaluated. In our study, bladder cancer risk was higher among men who drove trucks typically fueled by diesel (tractor-trailers) than among drivers of other types of trucks, and there was no increase for taxicab or bus drivers. Thus, our study supports the possibility of diesel exposure as the putative factor.

We found a significantly elevated risk of bladder cancer among male metal/plastic processing machine

operators which was attributable mainly to increased risk among operators of molding and casting machines (OR = 16.6). Risk appeared to be elevated in molders/casters of both metal and plastic materials. In a recent meta-analysis in predominantly iron and steel foundry workers [14], the summary risk estimate (SRE) for bladder cancer was 1.47 (0.99–2.2) for molders and 1.48 (1.14–1.91) for casters, higher for other occupational subgroups (furnacemen, heaters; rolling mill operators; fitters and finishers). Metal molders in our study primarily worked from the 1940s to the 1960s (only two individuals worked as molder/casters only after 1970). During this time period, the major mold operation was probably the oil sand process, which was based on linseed oil, bentonite, coal tar pitch, fuel oil, and asphalt; organic flours (e.g., wood) were used as additives. This resulted in thermal decomposition products of cristobalite (the bentonite), carbon monoxide, and polycyclic aromatic hydrocarbons (the organic binders) [15, 16]. Exposure to metals from the furnace, pouring areas, shakeout, and finishing areas was also likely.

Plastic molders and casters, in contrast, are not well studied. In a study from Italy, bladder cancer risk was elevated among workers in “plastics transformation” [17]. Also, Zahm et al. [18] found an elevated risk of bladder cancer among operators exposed to “dusty or hot processes” in the plastics industry. Others have found elevated bladder cancer risk among plastics

Table 5. Bladder cancer risk for men and women ever employed in *a priori* suspect occupations^{a,b}

<i>A priori</i> occupation	SOC codes	Cases ^c (n)	Controls ^c (n)	OR	95% CI	Trend (<i>P</i>)
Men						
Garage and/or gas station worker	873	19	15	1.7	0.8–3.4	
< 5 years		14	14	1.4	0.6–2.9	
5+ years		5	1	6.3	0.7–54.8	0.066
Gardener	5622	22	18	1.8	0.9–3.4	
< 5 years		16	15	1.6	0.8–3.4	
5+ years		6	3	2.5	0.6–10.5	0.190
Plumber	645	10	8	1.6	0.6–4.2	
< 5 years		4	3	2.0	0.4–9.1	
5+ years		6	5	1.4	0.4–4.8	0.512
Woodworker	683, 743, 763	24	19	1.4	0.7–2.6	
< 5 years		18	12	1.9	0.9–4.1	
5+ years		6	7	0.7	0.2–2.1	0.955
Women						
Hairdresser, barber	5252, 5253	4	6	2.1	0.5–8.0	
< 5 years		2	3	2.1	0.3–13.9	
5+ years		2	3	2.1	0.3–13.8	0.357

^a Adjusted for age and smoking.

^b Results presented for *a priori* occupations held by 10 men or 10 women and an association that was statistically significant or ≥ 1.3 . Table excludes occupations included on previous tables.

^c Number of men or women employed in each occupation.

workers in general [19–21]. However, most bladder cancer case-control studies report on the plastics and rubber industries combined. For molders of plastic materials, possible exposures include monomers, metals (from pigments), plasticizers, mold-releasing agents, lubricants, and thermal decomposition products.

Our study confirmed a previous report of elevated bladder cancer risk among male fabricators, assemblers, and handworkers [22]. This is a diverse occupational group composed, in our study, mainly of assemblers in a variety of industries; there was no clearly prominent industry. The data we gathered on participants’ work histories did not permit us to speculate on the specific exposures that may be responsible for the increased risk.

Women employed in marketing and sales occupations in our study had elevated bladder cancer risk. Other studies that have noted an excess risk among female salesworkers include “saleswoman and salesclerk, NEC” [23], “other saleswomen, shop assistants, and demonstrators” [24] and “car saleswomen” [25]. There have also been reports of elevated risk among sales/marketing occupations for both sexes combined [26, 27] and for men [7, 17, 22, 28–31]. These findings are typically attributed to chance, to confounding by smoking, or to unknown factors related indirectly to the job (e.g., environmental tobacco smoke, sedentary nature of the work, frequency of urination, or general lifestyle factors). In our study, risk was significantly

elevated among women in “other” retail sales occupations (sales clerks, counter clerks, cashiers). It is plausible that this type of work presents fewer opportunities for micturition, prolonging the contact time between the bladder mucosa and any urinary carcinogens that might be present. Data on urination frequency, which was not collected in our study, may help future studies elucidate the potential bladder cancer risk in sales workers.

In our study, women employed in health service occupations (predominantly nurses’ aides in hospitals and nursing homes, and a small number of dental assistants and health aides) were at elevated risk for bladder cancer. Related data from other studies are extremely sparse. Malker *et al.* [30] reported significant excess risk among male dental technicians in Sweden, and Dolin and Cook-Mozaffari [32] found no association among male hospital orderlies. To our knowledge, there are no previous reports of bladder cancer risk among female nurses’ aides. Exposure to chemotherapeutic agents may have contributed to the bladder cancer excess among nurses aides in our study. Excess secondary urinary tract malignancies have been observed in patients treated with certain antineoplastic drugs [33–35], and both the patients receiving antineoplastic drugs and the nurses administering them have exhibited mutagenicity in their urine [36]. Although nurses aides do not administer chemotherapy, exposure may occur through activities such as cleaning and disposal of equipment and

supplies, or contact with bodily fluids of patients undergoing chemotherapy. The extent to which this may have occurred among the nurses' aids in our study is unknown. We found a statistically significant interaction between smoking and working in health service occupations. However, this requires a cautious interpretation since it is difficult to explain and was based on a relatively small number of subjects.

We found an elevated bladder cancer risk among men and women employed as kitchen workers and cooks, although the associations were not statistically significant and previous studies have been inconsistent. For example, Cole [37] found a 55% excess among male cook, kitchen, and counter workers, and Steenland *et al.* [7] reported elevated risk among male cook supervisors. Yet several studies observed no excess risk among male cooks [13, 32, 38, 39] or both sexes combined [40]. Porru *et al.* [41] reported an 80% excess among male, but not female, cooks/waiters/bartenders. In the US National Bladder Cancer Study, the summary category of cook, baker, and food counter worker was not associated with an elevated risk for white men, white women, or black men [2, 23, 42], but there was a 60% nonsignificant increase for black male cooks [42]. Thus, the evidence that cooks or kitchen workers are at an excess bladder cancer risk remains weak.

The strengths of our study include the population-based design and ascertainment of complete occupational histories from direct interviews with all study

subjects, and the ability to adjust for smoking. A shortcoming was that information was collected only on job title and place of work, limiting our ability to examine previously-reported associations for specific industries or exposures (*e.g.*, dyestuffs workers and dye users, aromatic amine manufacturing workers, rubber workers, leather workers, and aluminum workers). Similar to other case-control studies of occupation, limitations also include the small number of people in many occupations. While we reduced the number of comparisons to some extent by restricting the analysis to occupations held by at least 15 participants of a single gender (ten for the *a priori* occupations), the large number of comparisons performed in the analysis leaves open the possibility of chance associations. Finally, job titles are only crude surrogates for exposures. An individual job title may be associated with a wide range of possible exposures, and grouping people who may be highly exposed with those potentially unexposed attenuates the strength of the association.

In conclusion, our study corroborates many previously reported associations between bladder cancer risk and various occupations. Particularly interesting findings warranting additional research are the strong association for male metal and plastic molding and casting machine operators, the elevated bladder cancer risk among female sales workers, and the enhanced risk among women in health service occupations, especially if they smoked.

Appendix A. *A priori* occupations with ORs < 1.3 in current study^a

Job title with elevated risk in previous study(ies)	SOC code(s) assigned by industrial hygienist	Men		Women	
		Cases ^b	Controls ^b	Cases ^b	Controls ^b
Armed services	91	235	283	6	12
Automobile mechanic	6111	17	21	–	–
Building services	524	29	30	8	20
Carpenter	6422	19	29	–	–
Checker, examiner, inspector, manufacturing, NEC	78	17	22	4	15
Clerical worker	462, 463, 464, 466, 469, 471	24	36	32	104
Construction labourer	871	13	13	–	–
Dry cleaning and laundry service	7658, 7657	5	5	–	–
Electrical and electronic workers	615, 6867	16	17	–	–
Electrical engineers	1633	6	13	–	–
Electricians, electrical, and electronic fitters	6432	7	10	–	–
Engineer	162, 163	29	55	–	–
Farmers	551	6	10	–	–
Farmers and farm laborers	551, 5612, 5613, 5614	42	53	–	–
Filer, polisher, sander, or buffer	7522, 6816	5	6	–	–
Food counter and fountain worker	5216	–	–	2	9
Forestry occupation	57	17	25	–	–
Guard or watchmen	514, 5133	13	17	–	–
Inspector, grader, weigher, construction foreman	631, 1472	3	8	–	–

Appendix A. (Continued)

Job title with elevated risk in previous study(ies)	SOC code(s) assigned by industrial hygienist	Men		Women	
		Cases ^b	Controls ^b	Cases ^b	Controls ^b
Janitor or cleaner	5244	26	24	–	–
Labourer	8769	54	58	2	12
Machine operator	75, 76	96	109	25	52
Machine tool operator	751, 752	12	15	–	–
Machinist	751, 752, 6813	29	37	–	–
Manager, administrator	12, 13	111	130	12	41
Manager: company manager or executive	121, 122, 123, 124, 125, 126, 132, 133, 134, 135, 136, 137, 139	108	122	12	37
Manager: marketing, advertising, public relations	125	28	34	3	9
Material moving equipment operators	831	10	15	–	–
Mechanic	61	56	67	–	–
Mechanic, other than vehicle	613, 614, 615, 616, 617	36	49	–	–
Mechanics/repairers, miscellaneous	617	5	13	–	–
Metal machinist	6813	18	22	–	–
Metal and plastic working machine operators	751, 752	12	15	–	–
News vendor	4365	4	7	–	–
Officials and administrators, public administration	11	11	18	3	8
Painter	6442, 7669	12	15	–	–
Painter, construction and maintenance	6442	7	11	–	–
Precision inspectors, testers, and graders	6881	5	6	–	–
Precision metal workers	681, 682	29	40	4	6
Printers	684, 765	8	14	–	–
Printing plant employee: press operators	7643, 7644, 7649, 6842, 6849	4	9	–	–
Private household services	50	–	–	8	19
Produce grader and packer	5625, 8761	3	7	–	–
Taxicab driver or chauffeur	8216	8	10	–	–
Teachers	22, 23	15	33	12	42
Teachers, secondary school	233	8	18	5	18
Textile industry: other winder or twister	7651	–	–	2	12
Textile worker	745, 7651, 7651, 7653, 7654, 7655, 7657, 7659	12	23	10	21
Waiter or waitress	5213	–	–	19	44
Welder	771	6	5	–	–

^a Table includes only those *a priori* occupations held by 10 men or 10 women in the current study.

^b Number of men or women employed in each occupation in the current study.

–: Occupation was held by fewer than 10 people of that gender in the current study.

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