Exhibit 238

Occupation and bladder cancer in a population-based case–control study in Northern New England

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ABSTRACT

Objectives We used data from a large, population-based case–control study in Maine, New Hampshire, and Vermont to examine relationships between occupation, industry and bladder cancer risk.

Methods Lifetime occupational histories were obtained by personal interview from 1158 patients newly diagnosed with urothelial carcinoma of the bladder in 2001–2004, and from 1402 population controls. Unconditional logistic regression was used to calculate ORs and 95% CIs, adjusted for demographic factors, smoking and employment in other high-risk occupations.

Results Male precision metalworkers and metalworking/plasticworking machine operators had significantly elevated risks and significant trends in risk with duration of employment (precision metalworkers: OR 2.2, 95% CI 1.4 to 3.4, p_{trend}=0.0065; metalworking/plasticworking machine operators: OR 1.6, 95% CI 1.01 to 2.6, p_{trend}=0.047). Other occupations/industries for which risk increased significantly with duration of employment included: for men, textile machine operators, mechanics/repairers, automobile mechanics, plumbers, computer systems analysts, information clerks, and landscape industry workers; for women, service occupations, health services, cleaning and building services, management-related occupations, electronic components manufacturing and transportation equipment manufacturing. Men reporting use of metalworking fluids (MWF) had a significantly elevated bladder cancer risk (OR 1.7, 95% CI 1.1 to 2.5).

Conclusions Our findings support the hypothesis that some component(s) of MWF may be carcinogenic to the bladder. Our results also corroborate many other previously reported associations between bladder cancer risk and various occupations. More detailed analyses using information from the study's job-specific questionnaires may help to identify MWF components that may be carcinogenic, and other bladder carcinogens associated with a variety of occupations.

What this paper adds

- Over 40 occupations have been associated with an elevated risk of bladder cancer in epidemiological studies, but the evidence is compelling for only a few.
- A large, population-based case–control study with lifetime occupational histories and detailed exposure assessment techniques provided the opportunity to further examine occupational risk factors for bladder cancer.
- Men reporting use of metalworking fluids (MWF) had a significantly elevated bladder cancer risk, supporting the hypothesis that these fluids contain bladder carcinogens and contribute to the often observed association between bladder cancer and metalworking.
- Significant findings were observed for many other occupations/industries, including: for men, textile machine operators, automobile mechanics, plumbers and landscape workers; and for women, health services, cleaning and building services, electronic components manufacturing and transportation equipment manufacturing.
- More detailed analyses using information collected in job-specific questionnaires administered in this study may help to identify components of MWF that may be carcinogenic, and other bladder carcinogens to which people are exposed in a variety of occupations.

INTRODUCTION

Occupational risk factors for bladder cancer have been examined in many studies. Although over 40 occupations have been associated with an elevated risk, the evidence is compelling for only a small number of occupations: dyestuffs workers and dye users, aromatic amine manufacturing workers, rubber workers, leather workers, painters, truck drivers and aluminium workers. There is strong evidence that certain aromatic amines are carcinogenic to the human bladder. Associations have been observed for several other occupational exposures, including polycyclic aromatic hydrocarbons (PAHs), diesel engine exhaust, leather dust, mineral oils, combustion and pyrolysis products, chlorinated solvents, creosote, herbicides/pesticides and asbestos.[1] We used interview data from a large, population-based case–control study in New England, where bladder cancer mortality rates have been elevated for decades,[2] to examine the relationships between occupation, industry and bladder cancer risk. This study builds upon earlier studies of bladder cancer and occupation in this region[3–5] by studying disease incidence rather than mortality and by using detailed exposure assessment techniques. The extent to which occupational exposures might explain the New England bladder cancer excess will be examined as part of

a broader effort integrating findings from this analysis with those for several other risk factors.

METHODS

Study population

The study was conducted in Maine, Vermont and New Hampshire. All residents newly diagnosed with a histologically-confirmed carcinoma of the urinary bladder (including carcinoma in situ) at ages 30–79 years between 1 September 2001 and 31 October 2004 (Maine and Vermont) or between 1 January 2002 and 31 July 2004 (New Hampshire) were eligible for study. Rapid patient ascertainment in each state was conducted using data from hospital pathology departments, hospital cancer registries and the state cancer registries. We interviewed 1213 cases (65% of 1878 eligible cases). Of non-participating cases, 50% refused, 22% were deceased, 12% were too ill, 5% did not speak English, 5% had a physician refusal and 5% were not locatable. Based on a diagnostic slide review by the study's expert pathologist (AS), we excluded 20 patients determined not to have bladder cancer and 23 patients with non-urothelial carcinoma, leaving 1170 cases.

Controls aged 30–64 years were selected randomly from Department of Motor Vehicle (DMV) records in each state, and controls aged 65–79 years were selected from beneficiary records of the Centers for Medicare and Medicaid Services (CMS). Controls were frequency matched to cases by state, gender and age at diagnosis or control selection (within 5 years). We interviewed 1418 (594 DMV and 824 CMS) controls (65% of eligible DMV and 65% of eligible CMS controls). Of non-participating controls, 70% and 65% of DMV and CMS controls, respectively, refused, 24% of DMV and 11% of CMS controls were not locatable, 3% of DMV and 10% of CMS controls did not speak English, 1% of DMV and 7% of CMS controls were too ill, and 1% of DMV and 7% of CMS controls were deceased.

All respondents gave written informed consent to participate in this study. The study protocol was approved by the National Cancer Institute Special Studies Institutional Review Board, as well as the human subjects review boards of each participating institution.

Questionnaire data

Individuals who agreed to participate were asked to complete a mailed residence and work history calendar before the home visit. During the home visit, a trained interviewer reviewed the calendar and administered a computer-assisted personal interview. The interviewer recorded all jobs held for at least 6 months since age 16, excluding unpaid jobs and absentee business ownership. For each job, participants were queried about the employer name and location, years job started and ended, type of business, products made or services provided, and the participant's main duties, tools used and chemicals handled. For certain occupations, job-specific questionnaires were administered to solicit detailed information about exposures of interest[6] (see online appendix A). The computer-assisted personal interview also covered demographics, tobacco use and other exposures.

A total of 1158 of 1170 cases (99%) and 1402 of 1418 controls (99%) were included in the analysis; the remainder had no qualifying jobs or were missing information on potential confounders.

Occupational coding and statistical analysis

We coded each job using the 1980 Standard Occupational Classification (SOC)[7] and the 1987 Standard Industrial Classification (SIC)[8] schemes. Using unconditional logistic regression models, we computed sex-specific ORs and 95% CIs for bladder cancer for each two-, three- and four-digit SOC and SIC code using SAS statistical software, version 9.1. For each OR, the reference group comprised those never employed in the occupation or industry. ORs were adjusted for age (<55, 55–64, 65–74, 75+ years), race (white only, Native American/white, other races), Hispanic ethnicity (yes/no), state, smoking status (never, occasional (<100 cigarettes over the lifetime), former, current) and employment in a high-risk occupation other than the one being analysed (ever/never). Occupations were identified as 'high-risk' (see online appendix B) for men and women separately if ORs in this study were 1.5 or higher prior to the high-risk occupation adjustment and 10 or more individuals were employed; however, if a three-digit occupational code met these criteria but had substantial variation in risk among the four-digit codes it comprised, we selected only those four-digit codes with elevated risk, regardless of the number of people employed. We further evaluated smoking effects by replacing smoking status with smoking duration (never smoked, smoked occasionally, smoked for <10 years, 10–19 years, 20–29 years, 30–39 years, 40–49 years, 50+ years) and found minimal changes in the ORs; therefore, the final models were adjusted for smoking status only. ORs and 95% CIs for ever/never employment in each SOC and SIC code are presented in the tables if the occupation or industry was held by at least 15 men or 15 women in our study and (1) had an OR that was either statistically significant or ≥2.0 or ≤0.5 in our study, or (2) is considered to be an a priori high-risk occupation (ie, an occupation with multiple reports of elevated risk in the literature and listed in Schottenfeld and Fraumeni's textbook).[1] Online appendices B and C provide complete results for ever/never employment in all occupations and industries held by our study participants.

We assessed risk by duration of employment for occupations and industries with a significant association for ever/never employed. In addition to the reference category (never held the job), two duration categories (with 5 or 10 years of employment as cut-points) were used if fewer than 50 people held the job, and three (with 5 and either 10 or 15 years of employment as cut-points) were used if there were 50+ people. Selection of cut-points was job specific, based on the distribution of years of employment. Tests of linear trend were performed by treating the median duration of employment among controls for each duration category as a continuous variable; participants who never held the job of interest were assigned a duration of zero.

For occupations with a significant positive trend in risk with increasing duration of employment, we examined the relationship between initial year of employment and bladder cancer risk if numbers permitted. We also tested for interactions between smoking and occupation by adding a cross-product term to the logistic model. Finally, because controls under age 65 were limited to those with driver's licences, we also restricted the cases under age 65 to those with a valid driver's licence at the time of diagnosis; the changes in the risk estimates were minimal and the results are not presented.

RESULTS

We focus mainly on occupations and industries with significant trends in risk with duration of employment. All statistically significant associations, both positive and negative, are indicated by asterisks in tables 1 and 2.

Risk by SOC code

Among men, bladder cancer risk was significantly elevated (table 1) and increased significantly with duration of employment (table 3) in several a priori high-risk occupations:

Table 1 Risk of bladder cancer by occupation (SOC), by sex, New England, 2001–2004†

		Men (n=895 cases, 1031 controls)				Women (n=263 cases, 371 controls)			
SOC	Occupation	Cases (n)	Cont (n)	OR	95% CI	Cases (n)	Cont (n)	OR	95% CI
A priori high-risk occupations									
141	Accountants, auditors, and other financial specialists	22*	51*	0.5*	0.3 to 0.9*	8	8	2.2	0.8 to 6.6
162–3	Engineers	55	85	0.7	0.5 to 1.1	1	0	—	—
	1634 Industrial engineers	12	7	2.2	0.8 to 5.8	0	0	—	—
29	Registered nurses	2	3	—	—	13	25	0.9	0.4 to 2.0
42	Sales occupations, commodities except retail	48	66	0.9	0.6 to 1.3	3	3	—	—
43	Sales occupations, retail	114	125	1.1	0.8 to 1.5	74	115	1.0	0.7 to 1.5
	4359 Salespersons, NEC	7	15	0.5	0.2 to 1.3	5	13	0.7	0.2 to 2.0
46–7	Administrative support occupations, including clerical	209	264	0.9	0.8 to 1.2	124*	191*	0.7*	0.5 to 0.99*
	462 Secretaries, stenographers and typists	4	12	0.3	0.1 to 1.1	58	66	1.3	0.8 to 2.0
	464 Information clerks	13*	9*	2.6*	1.1 to 6.5*	13	30	0.7	0.3 to 1.4
	471 Financial record processing occupations	18	35	0.6	0.3 to 1.2	42*	47*	2.4*	1.4 to 4.0*
	4713 Payroll and timekeeping clerks	4	12	0.4	0.1 to 1.3	2	6	0.3	0.1 to 1.5
	479 Miscellaneous administrative support occupations, including clerical	11	14	1.0	0.4 to 2.3	17*	46*	0.4*	0.2 to 0.8*
51	Protective service occupations	71	83	0.9	0.7 to 1.3	4	5	—	—
	5123 Firefighting occupations	13	21	0.7	0.3 to 1.5	0	0	—	—
	514 Guards	34	32	1.1	0.6 to 1.8	3	3	—	—
5214	Cooks, except short order	31	36	0.9	0.5 to 1.5	13	18	0.8	0.4 to 1.9
5215	Short-order cooks	15	10	1.6	0.7 to 3.7	3	6	—	—
5216	Food counter, fountain and related occupations	11	7	2.6	1.0 to 7.2	12	18	0.9	0.4 to 2.1
523	Health service occupations	29	29	1.3	0.7 to 2.3	38*	36*	2.5*	1.4 to 4.4*
524	Cleaning and building service occupations, except private household	82*	65*	1.8*	1.3 to 2.6*	28*	19*	3.7*	1.8 to 7.3*
	5242 Maids and housemen	2	1	—	—	17*	10*	2.5*	1.02 to 6.1*
	5244 Janitors and cleaners	70	52	1.4	1.0 to 2.1	11	7	2.7	0.9 to 8.0
5253	Hairdressers and cosmetologists	1	1	—	—	7	10	1.7	0.6 to 5.3
5622	Groundskeepers and gardeners, except farm	31	45	0.8	0.5 to 1.4	2	1	—	—
61	Mechanics and repairers	217*	212*	1.3*	1.04 to 1.6*	2	4	—	—
	611 Vehicle and mobile equipment mechanics and repairers	119*	110*	1.5*	1.1 to 2.0*	1	1	—	—
	6111 Automobile mechanics	59*	46*	1.6*	1.05 to 2.4*	0	0	—	—
	615 Electrical and electronic machinery repairers	58*	49*	1.5*	1.02 to 2.3*	0	1	—	—
64	Construction trades	186	204	1.1	0.8 to 1.3	5	1	—	—
	641 Brickmasons, stonemasons and hard tile setters	13	8	2.2	0.9 to 5.6	0	0	—	—
	6422 Carpenters	67	88	0.8	0.5 to 1.1	2	0	—	—
	6432 Electricians	19	20	1.1	0.6 to 2.1	0	0	—	—
	6442 Painters (construction and maintenance)	19	21	1.0	0.5 to 2.1	1	0	—	—
	645 Plumbers, pipefitters and steamfitters	33	25	1.5	0.8 to 2.5	0	0	—	—
681–2	Precision metalworkers	53*	37*	2.2*	1.4 to 3.4*	0	2	—	—
	6813 Machinists	23	17	1.6	0.8 to 3.1	0	1	—	—
683	Precision woodworkers	7	12	0.7	0.2 to 1.7	0	1	—	—
763	Woodworking machine operators and tenders	15	18	0.8	0.4 to 1.7	3	4	—	—
687	Precision food production occupations	15	24	0.7	0.3 to 1.4	2	0	—	—
	6871 Butchers and meat cutters	11	14	0.9	0.4 to 2.0	0	0	—	—
6931	Stationary engineers	11	8	1.5	0.6 to 3.9	0	0	—	—
73	Machine setup operators (metals and plastics)	14	7	2.3	0.9 to 5.9	2	0	—	—
75	Machine operators and tenders (metals and plastics)	58*	50*	1.6*	1.05 to 2.4*	7	6	—	—
	751–2 Metalworking and plasticworking machine operators and tenders	47*	35*	1.6*	1.01 to 2.6*	5	3	—	—
	7529 Miscellaneous metalworking/ plasticworking machine operators	14*	6*	2.8*	1.002 to 7.6*	0	1	—	—

Continued

Table 1 Continued

SOC	Occupation	Men (n=895 cases, 1031 controls)				Women (n=263 cases, 371 controls)			
		Cases (n)	Cont (n)	OR	95% CI	Cases (n)	Cont (n)	OR	95% CI
764	Printing machine operators and tenders	9	17	0.5	0.2 to 1.2	2	4	—	—
765	Textile, apparel and furnishings machine operators and tenders	46*	29*	2.0*	1.2 to 3.3*	27	32	1.0	0.6 to 1.9
77	Fabricators, assemblers and hand working occupations	109	104	1.1	0.8 to 1.5	36	40	1.4	0.8 to 2.3
	7714 Welders and cutters	21	20	1.0	0.5 to 2.0	1	1	—	—
821	Motor vehicle operators	202	208	1.0	0.8 to 1.3	8	9	1.0	0.3 to 2.8
	8212 Truck drivers, tractor-trailer	54	69	0.9	0.6 to 1.3	1	0	—	—
	8213 Truck drivers, heavy	57	47	1.3	0.9 to 2.0	1	0	—	—
	8214 Truck drivers, light	43	56	0.8	0.5 to 1.2	2	2	—	—
	8216 Taxicab drivers and chauffeurs	23	21	1.1	0.6 to 2.0	1	1	—	—
8243	Sailors and deckhands	19	13	1.7	0.8 to 3.6	0	0	—	—
873	Garage and service station related occupations	42	44	1.0	0.7 to 1.6	0	2	—	—
91	Military occupations	180*	170*	1.3*	1.02 to 1.7*	2	0	—	—
A posteriori high- and low-risk occupations									
1352	Managers, entertainment and recreation facilities	4*	13*	0.3*	0.1 to 0.97*	0	4	—	—
14	Management-related occupations	54*	95*	0.7*	0.5 to 0.9*	20*	20*	2.7*	1.3 to 5.5*
	144 Purchasing agents and buyers	7	15	0.5	0.2 to 1.2	2	3	—	—
1712	Computer systems analysts	13*	4*	4.4*	1.3 to 14*	0	2	—	—
20	Social, recreation and religious workers	18	28	0.8	0.4 to 1.6	13	8	2.4	0.9 to 6.5
	203 Social and recreation workers	10	15	0.7	0.3 to 1.8	12	7	2.6	0.9 to 7.7
	2032 Social workers	8	8	1.0	0.4 to 3.0	10	6	2.6	0.8 to 8.3
22	Teachers, college, university and other postsecondary institution	25	35	1.3	0.8 to 2.3	6	23	0.5	0.2 to 1.3
	223 Teachers, health specialties/ business/agriculture/art/music/English	11*	6*	3.9*	1.4 to 11*	3	13	0.6	0.1 to 2.1
232	Elementary school teachers	3	12	0.4	0.1 to 1.4	7	15	0.7	0.3 to 2.0
32	Writers, artists, performers and related workers	24	33	1.2	0.7 to 2.0	12*	8*	3.7*	1.4 to 10*
	322 Designers	5	16	0.4	0.2 to 1.3	7	5	—	—
372	Drafting occupations	28*	18*	2.0*	1.05 to 3.7*	0	2	—	—
473	Communications equipment operators	9	3	—	—	10	24	0.5	0.2 to 1.0
	4732 Telephone operators	6	1	—	—	9	22	0.4	0.2 to 1.1
474	Mail and message distribution occupations	44	43	1.2	0.8 to 2.0	8	7	2.4	0.8 to 7.4
478	Adjusters, investigators and collectors	13	16	1.5	0.7 to 3.2	9	6	2.4	0.8 to 7.3
50	Private household occupations	1	4	—	—	15*	16*	2.7*	1.2 to 6.1*
52	Service occupations, except private household and protective	216*	204*	1.5*	1.2 to 1.9*	125*	152*	1.6*	1.1 to 2.3*
58	Fishers, hunters and trappers	17	11	2.1	0.9 to 4.7	0	1	—	—
6157	Telephone line installers and repairers	14	8	2.2	0.8 to 5.5	0	0	—	—
6313	Supervisors, carpenters and related workers	5	14	0.4	0.1 to 1.1	0	0	—	—
78	Production inspectors, testers, samplers and weighers	29	41	0.8	0.5 to 1.3	14*	8*	3.6*	1.4 to 9.3*
	782 Production inspectors, checkers and examiners	16	25	0.6	0.3 to 1.3	12	6	2.2	0.7 to 6.7
81	Supervisors, transportation and material moving occupations	9	7	2.1	0.8 to 5.9	0	0	—	—

*Statistically significant association.
†Adjusted for age (<55, 55–64, 65–74, 75+ years), race (white only, Native American/white, other races), Hispanic ethnicity (yes/no), state (Maine, New Hampshire, Vermont), smoking status (never, occasional (<100 cigarettes over lifetime), former, current), and employment in high-risk occupations other than the one being analysed (ever/never).
Cont, Controls; NEC, not elsewhere classified; SOC, Standard Occupational Classification.

information clerks (SOC 464, OR 2.6, 95% CI 1.1 to 6.5, p_{trend}=0.011), mechanics and repairers (SOC 61, OR 1.3, 95% CI 1.04 to 1.6, p_{trend}=0.0030), vehicle and mobile equipment mechanics (SOC 611, OR 1.5, 95% CI 1.1 to 2.0, p_{trend}=0.0023), automobile mechanics (SOC 6111, OR 1.6, 95% CI 1.05 to 2.4, p_{trend}=0.030), precision metalworkers (SOC 681–2, OR 2.2, 95% CI 1.4 to 3.4, p_{trend}=0.0065), machine operators and tenders (metal and plastic) (SOC 75, OR 1.6, 95% CI 1.05 to 2.4, p_{trend}=0.023), metalworking/plasticworking machine operators (SOC 751–2, OR 1.6, 95% CI 1.01 to 2.6, p_{trend}=0.047) and textile/apparel/furnishings machine operators (SOC 765, OR 2.0, 95% CI 1.2 to 3.3, p_{trend}=0.0013). Plumbers/pipefitters/steamfitters (SOC 645), another a priori high-risk occupation, had a significant positive trend in risk (p_{trend}=0.032) and a non-significantly increased risk for ever/never employed (OR 1.5, 95% CI 0.8 to 2.5). The only a posteriori high-risk occupation with a significant duration trend was computer systems analysts (SOC 1712, OR 4.4, 95% CI 1.3 to 14, p_{trend}=0.021). Bladder

Table 2 Risk of bladder cancer by industry (SIC), by sex, New England, 2001–2004†

SIC	Industry	Men (n=895 cases, 1031 controls)				Women (n=263 cases, 371 controls)			
		Cases (n)	Cont (n)	OR	95% CI	Cases (n)	Cont (n)	OR	95% CI
078	Landscape and horticultural services	25*	14*	2.4*	1.2 to 4.8*	1	3	–	–
1629	Heavy construction, NEC	13	9	2.0	0.8 to 5.1	0	0	–	–
201	Meat products	11	4	2.8	0.8 to 9.4	1	2	–	–
202	Dairy products	8	16	0.4	0.2 to 1.0	2	0	–	–
205	Bakery products	6	12	0.4	0.2 to 1.3	0	1	–	–
361	Electric transmission and distribution equipment	4	12	0.3	0.1 to 1.1	3	0	–	–
367	Electronic components and accessories	38	31	1.4	0.8 to 2.3	25*	15*	2.2*	1.1 to 4.7*
	3674 Semiconductors and related devices	9	11	1.1	0.4 to 2.8	10	5	2.5	0.7 to 8.5
37	Transportation equipment	106	123	0.8	0.6 to 1.1	12*	3*	8.7*	2.0 to 37*
38	Instruments and related products	38	55	0.8	0.5 to 1.3	4	11	0.4	0.1 to 1.4
	382 Laboratory apparatus and analytical, optical, measuring and controlling instruments	7*	17*	0.4*	0.1 to 0.97*	1	3	–	–
39	Miscellaneous manufacturing industries	24	17	1.7	0.9 to 3.3	5*	13*	0.3*	0.1 to 0.98*
4215	Courier services, except by air	6	9	0.5	0.2 to 1.4	1	0	–	–
451	Air transportation, scheduled and air courier services	10	7	2.4	0.8 to 6.7	2	3	–	–
4813	Telephone communications, except radiotelephone	19	20	0.9	0.5 to 1.8	9	19	0.5	0.2 to 1.2
506	Electrical goods	6	13	0.4	0.2 to 1.2	1	1	–	–
5143	Dairy products, except dried or canned	14*	5*	3.3*	1.1 to 9.4*	0	0	–	–
5149	Groceries and related products, NEC	9*	20*	0.4*	0.2 to 0.9*	3	0	–	–
5211	Lumber and other building materials	8	15	0.5	0.2 to 1.2	1	2	–	–
5531	Auto and home supply stores	11*	23*	0.4*	0.2 to 0.8*	1	2	–	–
571	Home furniture and furnishing stores	8	16	0.5	0.2 to 1.2	9	4	–	–
	5712 Furniture stores	3*	13*	0.3*	0.1 to 0.97*	3	3	–	–
5813	Drinking places	4*	12*	0.3*	0.1 to 0.9*	1	2	–	–
596	Non-store retailers	7	15	0.5	0.2 to 1.3	5	12	0.6	0.2 to 1.8
599	Retail stores, NEC	6	14	0.4	0.1 to 1.0	5	4	–	–
62	Security, commodity brokers and service	3	13	0.3	0.1 to 1.0	3	1	–	–
6311	Life insurance	11	6	2.6	0.9 to 7.3	7	3	–	–
6531	Real estate agents and managers	16*	34*	0.5*	0.3 to 0.9*	7	9	1.1	0.3 to 3.5
70	Hotels, rooming houses, camps and other lodging	33*	57*	0.6*	0.4 to 0.9*	23	17	1.7	0.8 to 3.6
	7011 Hotels and motels	23*	46*	0.5*	0.3 to 0.9*	19	13	1.6	0.7 to 3.8
7629	Electrical and electronic repair shops, NEC	12*	4*	3.3*	1.01 to 11*	0	2	–	–
7699	Repair shops and related services, NEC	16	9	2.0	0.8 to 4.7	0	2	–	–
80	Health services	59	73	1.0	0.7 to 1.5	77*	119*	0.7*	0.5 to 0.99*
	805 Nursing and personal care facilities	4*	15*	0.3*	0.1 to 0.97*	32	32	1.0	0.6 to 1.8
81	Legal services	9	10	1.7	0.6 to 4.5	11	7	2.4	0.8 to 6.9
822	Colleges, universities, professional schools, junior colleges	54	64	1.2	0.8 to 1.8	16*	46*	0.4*	0.2 to 0.8*
	8221 Colleges and universities	52	61	1.2	0.8 to 1.9	16*	43*	0.5*	0.2 to 0.9*
	8231 Libraries	1	2	–	–	3	13	0.4	0.1 to 1.4
8361	Residential care	5	9	–	–	11	4	3.5	1.0 to 13
91	Executive, legislative and general government	11	16	1.0	0.4 to 2.2	13	11	2.0	0.8 to 4.9

*Statistically significant association.
†Adjusted for age (<55, 55–64, 65–74, 75+ years), race (white only, Native American/white, other races), Hispanic ethnicity (yes/no), state (Maine, New Hampshire, Vermont), smoking status (never, occasional (<100 cigarettes over lifetime), former, current) and employment in high-risk occupations other than the one being analysed (ever/never).
Cont, Controls; NEC, not elsewhere classified; SIC, Standard Industrial Classification.

cancer risk was significantly reduced among male accountants/auditors/financial specialists (SOC 141, OR 0.5, 95% CI 0.3 to 0.9), with a significant negative trend with duration of employment (p_{trend}=0.045).

Among women, bladder cancer risk was significantly elevated (table 1) and increased significantly with duration of employment (table 3) in management-related occupations (SOC 14, OR 2.7, 95% CI 1.3 to 5.5, p_{trend}=0.0018) and service occupations, except private household and protective (SOC 52, OR 1.6, 95% CI 1.1 to 2.3, p_{trend}=0.031). Among the service occupations, risks were elevated in health services (SOC 523, OR 2.5, 95% CI 1.4 to 4.4, p_{trend}=0.0013) and in cleaning and building service occupations (SOC 524, OR 3.7, 95% CI 1.8 to 7.3, p_{trend}=0.0010) (both a priori high-risk occupations). Women in miscellaneous administrative support occupations (SOC 479) had a significantly reduced risk (OR 0.4, 95% CI 0.2 to 0.8) with a significant duration effect (p_{trend}=0.043).

Risk by SIC code

Men in the landscape and horticultural services industry (SIC 078) had a significantly elevated risk of bladder cancer (OR 2.4, 95% CI 1.2 to 4.8) (table 2) and a significant positive trend in risk

Table 3 Risk of bladder cancer by duration of employment for occupations and industries with significant duration trends, New England, 2001–2004* †

		Duration (years)	Cases (n)‡	Cont (n)‡	OR	95% CI	p Value (trend test)
Occupation, men							
A priori high-risk occupations							
SOC 141	Accountants, auditors and other financial specialists	<5	7	13	0.6	0.2 to 1.5	
		5–<15	6	17	0.5	0.2 to 1.4	
		15+	9	21	0.5	0.2 to 1.1	0.045
SOC 464	Information clerks	<5	8	8	1.5	0.5 to 4.2	
		≥5	5	1	14.5	1.6 to 129	0.011
SOC 61	Mechanics and repairers	<5	60	65	1.1	0.8 to 1.6	
		5–<15	65	71	1.1	0.8 to 1.6	
		15+	92	76	1.7	1.2 to 2.4	0.0030
SOC 611	Vehicle and mobile equipment mechanics and repairers	<5	41	41	1.4	0.9 to 2.2	
		5–<15	38	37	1.2	0.7 to 2.0	
		≥15	40	32	2.1	1.3 to 3.5	0.0023
SOC 6111	Automobile mechanics	<5	25	22	1.4	0.7 to 2.5	
		5–<15	17	12	1.6	0.7 to 3.4	
		≥15	17	12	2.1	0.98 to 4.6	0.030
SOC 645	Plumbers, pipefitters and steamfitters	<5	11	10	1.0	0.4 to 2.5	
		5–<15	8	10	1.2	0.4 to 2.7	
		15+	14	5	3.3	1.1 to 9.6	0.032
SOC 681–2	Precision metalworkers	<5	14	11	1.9	0.8 to 4.3	
		5–<10	19	12	2.4	1.1 to 5.1	
		10+	20	14	2.2	0.98 to 4.6	0.0065
SOC 75	Machine operators and tenders (metal and plastic)	<5	33	29	1.6	0.95 to 2.8	
		5–<10	10	12	0.8	0.3 to 2.0	
		10+	15	9	2.8	1.2 to 6.6	0.023
SOC 751–2	Metalworking/plasticworking machine operators/tenders	<5	26	22	1.5	0.8 to 2.7	
		5–<10	8	6	1.4	0.4 to 4.1	
		10+	13	7	2.4	0.9 to 6.3	0.047
SOC 765	Textile/apparel/furnishing machine operators/tenders	<5	24	18	1.6	0.8 to 3.1	
		5–<10	9	9	1.2	0.4 to 3.1	
		10+	13	2	10.3	2.2 to 48	0.0013
A posteriori high-and low-risk occupations							
SOC 1712	Computer systems analysts	<10	5	2	2.7	0.5 to 15	
		10+	8	2	6.3	1.2 to 33	0.021
Occupation, women							
A priori high-risk occupations							
SOC 523	Health service occupations	<5	14	19	1.6	0.7 to 3.5	
		5–<10	14	10	3.0	1.2 to 7.3	
		10+	10	7	4.4	1.5 to 12	0.0013
SOC 524	Cleaning and building service occupations, except private household	<5	12	9	3.0	1.2 to 7.9	
		5+	16	10	4.4	1.7 to 11	0.0010
A posteriori high- and low-risk occupations							
SOC 14	Management-related occupations	<10	10	16	1.6	0.7 to 3.9	
		10+	10	4	7.1	2.0 to 25	0.0018
SOC 479	Miscellaneous administrative support occupations, including clerical	<5	11	27	0.5	0.2 to 1.2	
		5–<15	5	11	0.4	0.1 to 1.4	
		15+	1	8	0.2	0.02 to 1.6	0.043
SOC 52	Service occupations, except private household and protective	<5	55	74	1.4	0.9 to 2.3	
		5–<15	40	42	1.7	1.01 to 2.9	
		15+	30	36	1.9	1.06 to 3.5	0.031
Industry, men							
SIC 078	Landscape and horticultural services	<5	9	9	1.8	0.7 to 4.7	
		5+	16	5	3.3	1.1 to 9.6	0.023
SIC 6531	Real estate agents and managers	<5	6	13	0.5	0.2 to 1.4	
		5–<10	6	5	1.4	0.4 to 4.9	
		10+	4	16	0.2	0.1 to 0.7	0.011
SIC 805	Nursing and personal care facilities	<5	4	4	1.4	0.3 to 6.0	
		5+	0	11	–	–	0.037
Industry, women							
SIC 367	Electronic components and accessories industry	<5	11	9	1.6	0.6 to 4.3	
		5+	14	6	3.3	1.1 to 9.9	0.028

Continued

Table 3 Continued

		Duration (years)	Cases (n)‡	Cont (n)‡	OR	95% CI	p Value (trend test)
SIC 37	Transportation equipment industry	<5	7	0	—	—	
		5+	5	3	5.2	0.98 to 28	0.023
SIC 822	Colleges, universities, professional school, junior college	5	11	20	0.8	0.3 to 1.8	
		5–<15	5	7	0.7	0.2 to 2.5	
		15+	0	19	—	—	0.0079
SIC 8221	Colleges and universities	5	11	18	0.9	0.4 to 2.2	
		5–<15	5	9	0.5	0.1 to 1.7	
		15+	0	16	—	—	0.012

*Table includes only SOC and SIC codes with a significant association in table 1 or table 2 and a significant trend in risk with duration of employment. Plumbers (SOC 645) are included despite the lack of statistical significance in table 1 because this is an a priori high-risk occupation with a significant trend in risk with duration of employment.
†Adjusted for age (<55, 55–64, 65–74, 75+ years), race (white only, Native American/white, other races), Hispanic ethnicity (yes/no), state (Maine, New Hampshire, Vermont), smoking status (never, occasional (<100 cigarettes over lifetime), former, current) and employment in high-risk occupations other than the one being analysed (ever/never).
‡Number of men or women employed in each occupation or industry for the specified duration.
Cont, Controls; SIC, Standard Industrial Classification; SOC, Standard Occupational Classification.

with duration of employment (p_{trend}=0.023) (table 3), as did women in the electronic components and accessories industry (SIC 367, OR 2.2, 95% CI 1.1 to 4.7, p_{trend}=0.028) and the transportation equipment industry (SIC 37, OR 8.7, 95% CI 2.0 to 37, p_{trend}=0.023). Significant reductions in risk with significant duration effects were observed for men working as real estate agents/managers (SIC 6531, OR 0.5, 95% CI 0.3 to 0.9, p_{trend}=0.011) and in nursing and personal care facilities (SIC 805, OR 0.3, 95% CI 0.1 to 0.97, p_{trend}=0.037) and for women working in colleges and universities (SIC 8221, OR 0.05, 95% CI 0.2 to 0.9, p_{trend}=0.012).

Risk by decade first employed

The overall increased risk among vehicle and mobile equipment mechanics, particularly automobile mechanics, was limited to men who began working before 1970 and was highest for those first employed before 1950 (table 4). Only those plumbers/pipefitters/steamfitters first employed before 1960 were at elevated risk. The elevated risk for metalworking/plasticworking machine operators was evident only among men who first held this job before 1970. Men who first operated textile/apparel/furnishing machines in the 1950s had an eightfold risk of bladder cancer that was statistically significant, but there was no discernable pattern in risk by year of first employment.

Interactions with cigarette smoking

The only occupation with a statistically significant smoking interaction was precision metalworking (table 5). Although the interaction was not significant for metalworking/plastic working machine operators, the joint effect was stronger than an additive model would yield, with a sixfold risk among smokers compared to non-smoking men never employed in that occupation. The elevated risk observed among male precision metalworkers and metalworking/plasticworking machine operators was evident only among smokers.

Exposure to metalworking fluids

The excess risk of bladder cancer among male precision metalworkers and metalworking/plasticworking machine operators prompted us to explore the association between metalworking fluids (MWF) and bladder cancer risk. These complex chemical mixtures are used as coolants and lubricants in the machining process and are characterised as: straight oils (typically mineral oil), soluble oils, semi-synthetic fluids (mineral oil emulsified in water) and synthetic fluids (water with organics and additives; no oil content). Using information from the occupational histories and job-specific questionnaires, we grouped study participants into four mutually exclusive categories: (1) people reporting use of MWF in a job-specific questionnaire; (2) people assessed as having possible exposure to MWF by the study's industrial hygienist (PS); (3) people assessed as having no exposure to MWF, but possible exposure to mineral oil; and (4) people assessed as having no exposure to either MWF or mineral oil (referent group). We observed statistically significant elevations in risk among men exposed to MWF (OR 1.7, 95% CI 1.1 to 2.5) and those with possible exposure to mineral oil (OR 1.3, 95% CI 1.1 to 1.7) (table 6).

DISCUSSION

Several occupations and industries were associated with a significantly elevated risk of bladder cancer in this study. Of particular note are the findings for precision metalworkers and metalworking/plasticworking machine operators (most of whom worked with metals). There is strong a priori evidence of an excess bladder cancer risk among metalworkers,[4 9–27] and this has been widely hypothesised as being attributable to MWF exposure. In our study, reported use of MWF carried a 70% excess risk of bladder cancer that was statistically significant, adding to the evidence that some of these fluids contain bladder carcinogens. However, changes over time in the composition and prevalence of use of the different MWF make it difficult to identify the components potentially associated with bladder cancer.

The early, 'straight' MWF were typically mineral oils that contained PAHs, one class of possible bladder carcinogens.[17 28 29] PAH removal began in the 1950s[30] and levels were drastically lower by the mid-1980s[31]; however, small amounts may be created during machining.[32] Synthetic MWF, first marketed in the 1950s,[31] contained nitrites and amine additives for corrosion inhibition, often leading to the formation of N-nitrosamines,[32 33] which are bladder carcinogens in animal models.[34] Although nitrite was eliminated as an additive in the 1980s,[31] nitrosamines are still found at low levels.[35] Synthetic MWF may also contain N-phenyl-2-naphthylamine[32] and other additives and contaminants. In our study, only those metalworking/plasticworking machine operators first employed before 1970 had an elevated risk, but it is not possible to distinguish between secular changes in exposure and latency effects in this study. A recent cohort study of automotive workers in Michigan found that exposure to straight MWF increased bladder cancer risk but was unable to determine whether this was attributable to PAH exposure; synthetic MWF were not associated with an elevated risk of bladder cancer in that study.[36] Also noteworthy in our study were the significant interaction between smoking and precision

Table 4 Risk of bladder cancer by year of first employment among men, selected occupations, New England, 2001–2004*

	Year started employment	Cases (n)	Controls (n)	OR (95% CI)
Men				
Vehicle and mobile equipment mechanics (SOC 611)	<1950	22	15	2.3 (1.1 to 4.6)
	1950–59	37	33	1.8 (1.1 to 3.0)
	1960–69	32	27	1.5 (0.9 to 2.6)
	1970–79	18	20	1.2 (0.6 to 2.4)
	1980+	10	15	0.7 (0.3 to 1.8)
Automobile mechanics (SOC 6111)	<1950	12	4	4.4 (1.3 to 14)
	1950–59	14	12	1.6 (0.7 to 3.7)
	1960–69	17	11	1.8 (0.8 to 4.1)
	1970–79	10	11	0.9 (0.4 to 2.3)
	1980+	6	8	0.9 (0.3 to 2.9)
Plumbers, pipefitters and steam fitters (SOC 645)	<1950	7	2	3.1 (0.6 to 16)
	1950–59	11	5	3.4 (1.1 to 10)
	1960–69	7	6	1.3 (0.4 to 4.1)
	1970–79	3	6	0.6 (0.1 to 2.6)
	1980+	5	6	0.6 (0.2 to 2.1)
Precision metalworkers (SOC 681–2)	<1950	9	8	1.6 (0.6 to 4.5)
	1950–59	22	13	3.0 (1.4 to 6.2)
	1960–69	12	7	2.2 (0.8 to 6.0)
	1970–79	5	6	1.1 (0.3 to 3.8)
	1980+	5	3	2.6 (0.6 to 12)
Metalworking and plasticworking machine operators and tenders (SOC 751–2)	<1950	5	4	1.9 (0.5 to 7.4)
	1950–59	19	13	1.9 (0.9 to 4.1)
	1960–69	12	6	2.8 (0.98 to 7.8)
	1970–79	8	8	0.7 (0.3 to 2.1)
	1980+	3	4	0.9 (0.2 to 4.7)
Textile, apparel, and furnishing machine operators and tenders (SOC 765)	<1950	13	9	2.0 (0.8 to 4.8)
	1950–59	18	4	8.5 (2.7 to 27)
	1960–69	8	11	0.6 (0.2 to 1.5)
	1970+	7	5	1.6 (0.5 to 5.2)
Women				
Health service occupations (SOC 523)	<1960	6	7	2.2 (0.7 to 7.1)
	1960–69	7	10	1.9 (0.6 to 5.4)
	1970–79	11	6	4.7 (1.6 to 14)
	1980+	14	13	2.2 (0.9 to 5.2)
Cleaning and building service occupations, except private household (SOC 524)	<1970	10	4	5.5 (1.6 to 19)
	1970–79	5	7	2.4 (0.7 to 8.5)
	1980+	13	8	3.6 (1.3 to 9.9)

*Table shows three- and four-digit occupational codes with significant positive trends in risk with duration of employment. Computer system analysts and information clerks are excluded because of small numbers. Adjusted for age (<55, 55–64, 65–74, 75+ years), race (white only, Native American/white, other races), Hispanic ethnicity (yes/no), state (Maine, New Hampshire, Vermont), smoking status (never, occasional (<100 cigarettes over lifetime), former, current) and employment in high-risk occupations other than the one being analysed (ever/never).
SOC, Standard Occupational Classification.

metalworking, and the observation that the increased bladder cancer risk was observed largely among smokers.

The trend in risk with duration of employment among male operators of textile/apparel/furnishing machines was highly statistically significant (p_{trend}=0.0013), with a 10-fold risk for long-term employment. Most of these jobs were in the textile industry or the leather industry, with higher risk in the latter (OR 3.3, 95% CI 1.4 to 8.0) than the former (OR 1.6, 95% CI 0.8 to 3.3) (not shown). Most of the textile machine operators in the leather industry worked in shoe manufacturing, where there are many potential exposures; leather dust and solvents are the most common. Many investigators have reported elevated bladder cancer risk among shoemakers/repairers,[12 13 29 37–39] but it is unclear whether these studies included shoe manufacturers. Machine operators in the textile industry worked mostly in wool or cotton mills operating winding/twisting machines or knitting/weaving machines. The excess risk observed among operators of these types of machines is consistent with several previous studies.[17 40–42] Chemicals used in spinning and weaving areas have included mineral oils, polymers and sizing agents.[42 43]

The bladder cancer excess risk observed among male mechanics and repairers, particularly automobile mechanics, has been reported previously.[9 12 17 23 27 29 44] In our study, only those who started this work before 1970 had elevated risk. This could indicate that exposure to a carcinogen has diminished over time, or it could be a latency effect. The work environment of mechanics may involve exposure to many substances, including asbestos, oils and greases, metal dust, welding and soldering fumes, solvents, machining fluids and paints.[10 12 27 44–46]

Men working as plumbers for 15 years or more had a significantly elevated risk of bladder cancer in our study. Previous studies of plumbers have been inconsistent, with some reporting significant bladder cancer excesses[18 27] and others reporting non-significant excesses[4 10 37 47] or null findings.[12 17 41 44 46] Plumbers

Table 5 Risk of bladder cancer by cigarette smoking and employment in selected occupations, New England, 2001–2004*

Occupation	Smoking status: Never smoked, OR (95% CI)	Smoking status: Smoked, OR (95% CI)	p Value for interaction
Men			
Vehicle and mobile equipment mechanics (SOC 611)			
No	1.0 (ref)	3.0 (2.3 to 3.9)	
	102/277†	674/644	
			0.83
Yes	1.5 (0.7 to 3.0)	4.7 (3.2 to 7.0)	
	12/28	107/82	
Automobile mechanics (SOC 6111)			
No	1.0 (ref)	3.1 (2.4 to 3.9)	
	107/293	729/692	
			0.78
Yes	1.8 (0.7 to 4.9)	4.8 (2.9 to 8.0)	
	7/12	52/34	
Precision metalworker (SOC 681–682)			
No	1.0 (ref)	2.9 (2.2 to 3.7)	
	109/287†	733/707	
			0.021
Yes	0.7 (0.3 to 2.1)	8.6 (4.8 to 15)	
	5/18	48/19	
Metalworking/plasticworking machine operator (SOC 751–752)			
No	1.0 (ref)	2.9 (2.3 to 3.8)	
	108/289	740/707	
			0.13
Yes	0.9 (0.3 to 2.4)	6.3 (3.5 to 12)	
	6/16	41/19	
Textile, apparel and furnishing machine operators (SOC 765)			
No	1.0 (ref)	3.1 (2.4 to 3.9)	
	109/299	740/703	
			0.48
Yes	3.0 (0.9 to 10)	5.6 (3.2 to 10)	
	5/6	41/23	
Women			
Health service occupations (SOC 523)			
No	1.0 (ref)	3.3 (2.2 to 4.9)	
	47/152	178/183	
			0.17
Yes	4.4 (1.7 to 12)	6.7 (3.4 to 13)	
	9/11	29/25	
Cleaning and building service occupations, except private household (SOC 524)			
No	1.0 (ref)	3.0 (2.0 to 4.4)	
	51/156	184/196	
			0.84
Yes	3.5 (1.03 to 12)	9.0 (4.0 to 20)	
	5/7	23/12	

*Table shows three- and four-digit occupational codes with significant positive trends with duration of employment. Computer system analysts, information clerks and plumbers are excluded because of small numbers. Adjusted for age (<55, 55–64, 65–74, 75+ years), race (white only, Native American/white, other races), Hispanic ethnicity (yes/no), state (Maine, New Hampshire, Vermont) and employment in high-risk occupations other than the one being analysed (ever/never).
†Cases/controls.
SOC, Standard Occupational Classification.

Table 6 Risk of bladder cancer by exposure to metalworking fluids (MWF) among men, New England, 2001–2004*

	Cases (n)†	Controls (n)†	OR (95% CI)
Unexposed to MWF and mineral oil	264	365	1.0 (ref)
Exposed to MWF	68	53	1.7 (1.1 to 2.5)
Possibly exposed to MWF	186	219	1.1 (0.9 to 1.5)
Unexposed to MWF, possibly exposed to mineral oil	376	392	1.3 (1.1 to 1.7)

*Adjusted for age (<55, 55–64, 65–74, 75+ years), race (white only, Native American/white, other races), Hispanic status (yes/no), state (Maine, New Hampshire, Vermont), smoking status (never, occasional (<100 cigarettes over lifetime), former, current) and employment in high-risk occupations other than those involving MWF or mineral oil exposure (ever/never).
†Table excludes one case and two controls whose exposure status could not be determined.
MWF, Metalworking fluids.

have been reported to be exposed to many hazardous materials (eg, lead and other welding fumes, various solvents, tar, greases and asbestos), making it difficult to identify putative agents. Only those men who worked as plumbers before 1960 had an excess bladder cancer risk.

Risk was significantly elevated among men in the landscape and horticultural services industry, consistent with previous reports of excess bladder cancer risk among nursery workers, gardeners and lawn care service employees.[9 12 14 17 25 48 49] Although it has been postulated that exposure to pesticides and/or fertilisers might be responsible, the evidence is conflicting; some studies of pesticides and fertilisers reported an elevated risk,[14 17 50–54] while others did not.[11 12 55 56]

We observed a significant, twofold risk of bladder cancer among women in the electronic components and accessories industry that was attributable mainly to the manufacture of semiconductors and related devices. Employment in computer manufacturing, a related industry, was identified as a high-risk industry in Detroit women,[57] but a study of cancer incidence among male and female workers in a semiconductor manufacturing plant and a plant manufacturing computer hard drives and other electronic storage devices did not observe a bladder cancer excess.[58] Workers in the semiconductor and computer manufacturing industries may have been exposed to a variety of known or suspected carcinogens, including metals (arsenic, nickel, chromium), electromagnetic fields, asbestos, acids and various solvents.[58 59]

Risk was not significantly elevated among male construction/maintenance painters in our study, contrary to several previous studies.[23 27 60 61] However, when we identified men who had worked as painters (construction and maintenance painters; coating/painting/spraying machine operators; painting supervisors; or hand painting, coating and decorating occupations) and whose job titles or reported duties, tools, or exposures indicated that they had performed spray painting, there were many more cases (n=14) than controls (n=5). Several other investigators have described elevated risks for spray painters,[11 12 14 52] who have been reported to be exposed to many known or suspected carcinogens, including solvents and metals.

The strengths of our study include the population-based design and ascertainment of complete occupational histories from direct interviews with study participants, and the ability to adjust for smoking, employment in high-risk occupations and other risk factors. Limitations include the small number of people in many occupations and industries, and the large number of comparisons performed, allowing for chance associations. We reduced the number of comparisons and therefore the likelihood of chance findings to some extent by restricting the analysis to occupations held by at least 15 participants of a single gender, but it is likely that some of the significant associations reported here arose by chance. The 65% participation rate for cases and controls can be viewed as a limitation; however, because study participation is unlikely to have differed between cases and controls in an exposure-dependent manner, we do not believe that this led to bias in the risk estimates. Assigning SOC and SIC codes was challenging for some jobs

because of limitations in the information available from the interview; coders were blinded to case–control status and any misclassification was likely to be non-differential. Finally, occupation and industry titles are only a crude surrogate for exposures. An individual job or industry title may be associated with a wide range of exposures, and grouping people with a given job title who may be highly exposed with those potentially unexposed attenuates the strength of an association.

In conclusion, our results lend support to the hypothesis that some as yet unidentified components of MWF are carcinogenic to the bladder in humans and corroborate many other previously-reported associations between bladder cancer risk and various occupations. More detailed analyses using information collected in job-specific questionnaires administered in this study may help to identify components of MWF that may be carcinogenic, and other bladder carcinogens to which people are exposed in a variety of occupations.

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Competing interests None.

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