

Exhibit 325

Occupation and Bladder Cancer: A Population-Based, Case–Control Study in Iowa

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While considerable efforts have been made to investigate the role of occupation and industry in the risk of bladder cancer, many reported associations have not been consistent, and strong evidence of increased risk is apparent for few occupational groups. To further examine the issue, a large, population-based, case–control study was conducted in the state of Iowa among both men and women. A total of 1452 incident bladder cancer cases and 2434 controls were included in the study. Occupational history was collected from respondents for each job held for 5 years or longer since age 16. Among men, excess risk was observed for industries including plumbing, heating, and air conditioning (odds ratio [OR], = 2.2; 95% confidence interval [CI], 1.0 to 5.0); rubber and plastic products (OR = 3.1; 95% CI, 1.2 to 8.5), motor vehicle parts and supplies (OR = 4.5; 95% CI, 1.2 to 16.5), and occupations including supervisors for transportation and material moving (OR = 6.5; 95% CI, 1.4 to 29.9), material-moving-equipment operators (OR = 1.9; 95% CI, 1.0 to 3.6), automobile mechanics (OR = 1.6; 95% CI, 1.0 to 2.6), painters (OR = 2.7; 95% CI, 1.0 to 7.7), and metal- and plastic-working machine operators (OR = 2.0; 95% CI, 1.1 to 3.4). Among women, significant excess risk was observed for secondary school teachers and record clerks. Housekeepers and butlers and workers in laundering and dry cleaning were also at increased risk. In conclusion, these results suggest that occupational exposures may play a significant role in the risk of bladder cancer. (J Occup Environ Med. 2002;44:685–691)

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Bladder cancer is the most common malignant tumor of the urinary tract. It is estimated that 53,200 new cases will be diagnosed and 12,200 will die of the disease in the United States in the year 2000.¹ Environmental and occupational exposures have been implicated as risk factors for urinary bladder cancer.² Occupations and industries linked to bladder cancer include employment as a painter, printer, mechanic, machinist, metal worker, textile worker, truck driver, and chemical worker and employment in industries involving rubber, dye, leather, and petrochemical production; coke-oven processing; plastics and epoxy production; and hairdressing.^{3–7}

In spite of considerable efforts to investigate the role of occupation and industry, many reported associations have not been consistently found, and strong evidence of increased risk is apparent for few occupational groups. Furthermore, as pointed out by Silverman et al,⁸ the risk of bladder cancer associated with occupational exposures changes over time and from population to population: there is a need to exercise continued vigilance to identify new high-risk occupations and to determine which occupations are no longer associated with risk. In this large, population-based, case–control study of bladder cancer in the state of Iowa, we examined the role of occupation and industry on the risk of bladder cancer in both men and women.

Methods

Study Population

Detailed information regarding the study design has been described else-

where.⁹ In brief, a total of 1716 histologically confirmed incident bladder cancer cases, aged 40 to 85, was identified by the State Health Registry of Iowa in the years 1986 to 1989. Eligible cases were residents of Iowa and without previous diagnosis of a malignant neoplasm. Of the 1716 cases, 1452 (85%) participated in the study (1135 men and 317 women). Both in situ and invasive bladder cancers were included because they appear to share the same risk factors,¹⁰ and they are difficult for cancer surveillance systems to accurately separate.¹¹

A total of 2434 (1601 men and 833 women) population-based controls was frequency-matched by gender and 5-year age group to all cases in a larger study, which also included cancers of the brain, kidney, pancreas, colon, and rectum. The matching ratio for bladder cancer cases was approximately 1.7:1. Controls under the age of 65 were randomly selected from computerized state driver's license records. Controls aged 65 years and older were selected from US Health Care Financing Administration listings. As with the cases, persons with a previous cancer diagnosis were excluded from consideration as controls. The participation rate was 82% for controls younger than 65 and 80% for those aged 65 and older.

Data Collection

After physician consent was obtained for the cases, subjects were first contacted by mail and then by telephone. A postal questionnaire was used to collect detailed information. Of the 1452 cases, 1309 completed the mailed questionnaire. Among those who did not complete the mailed questionnaire, 87 cases completed a full-length telephone interview, and 56, an abbreviated telephone interview. Of the 2434 controls, 2164 completed the mailed questionnaire; 102, a telephone interview; and 168, an abbreviated telephone interview. Proxies completed the questionnaires for 156 cases who

had died or were not competent to participate. All control questionnaires (with two exceptions) were completed directly by the study subjects.

Respondents were asked to report each job held for 5 years or longer since age 16. For each job reported, we asked for job title, industry or type of business, the year when the job began and ended, and activities or duties associated with each job. In addition, respondents were asked to report the usual occupation that they had held during most of their adult life and the main activities and duties of the job. Job titles and industries obtained from the occupational history questions were subsequently coded according to the Standard Industry Classification¹² (SIC) and the Standard Occupational Classification Manual¹³ (SOC) schemes. Information on demographic factors, residence, smoking, past medical history, and first-degree family history of bladder cancer and other potential risk factors was also collected.

Data Analysis

The risk of bladder cancer associated with employment in various occupations and industries was calculated separately for men and women by using unconditional logistic regression models. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated using SAS statistical software.¹⁴ ORs were calculated for all two-digit, three-digit, and four-digit SOC codes and SIC codes when there were three or more exposed cases of one gender. We evaluated the risk of bladder cancer by duration of employment in various SOC and SIC categories, categorized into two groups (<10 years and ≥ 10 years). The reference category was composed of subjects not employed in the occupation or industry of interest.

The following potential confounders, which showed an impact on the observed ORs, were included in the final regression models: age (40 to 54, 55 to 64, 65 to 74, 75 to 85

years), lifetime pack-years of cigarette smoking (0, <25, 25 to 50, >50), and having a first-degree relative with bladder cancer (yes/no). Additional adjustment for education, frequency of strenuous or moderate exercise, duration of living in a residence served by chlorinated surface water, population size of places of residence (lifetime average), and other cancer in a first-degree relative did not result in material change to the observed associations and were therefore not included in the final models.

Results

Table 1 shows how age, smoking habit, and having a first-degree relative with bladder cancer were distributed among male and female cases and controls. Both age and smoking habit, risk factors for bladder cancer, were controlled for in all subsequent analyses. A significantly higher proportion of cases than controls reported having a first-degree relative with bladder cancer among both men and women, and a summary variable for this factor was also included in logistic regression models.

Table 2 presents occupations and industries, by two-, three-, or four-digit SIC and SOC codes, that showed statistically significant associations for bladder cancer among men, either overall or in one of the duration categories. Employment in the plumbing, heating, and air conditioning industries was associated with an increased risk of bladder cancer, as was working in industries producing rubber and plastic products, particularly among those with longer periods of employment. Employment in several industries and occupations where exposure to gasoline- or diesel-engine exhausts was likely showed a significantly increased risk of bladder cancer. These included the railroad transportation industry for 10 or more years, employment as an automotive dealer or at an automotive service station for 10 or more years, supervisors for transportation and material moving,

TABLE 1

Number and Proportion (%) of Bladder Cancer Cases and Controls Based on Selected Characteristics

Factor	Men		Women	
	Case (%)	Control (%)	Case (%)	Control (%)
Age (yr)				
40-54	122 (10.7)	149 (9.3)	31 (9.8)	93 (11.2)
55-64	252 (22.2)	358 (22.4)	64 (20.2)	190 (22.8)
65-74	447 (39.4)	629 (39.3)	105 (33.1)	276 (33.1)
75-85	314 (27.7)	465 (29.0)	117 (36.9)	274 (32.9)
Level of education (yr)				
≤8	304 (26.8)	392 (24.5)	50 (15.8)	115 (13.8)
9-11	196 (17.3)	203 (12.7)	40 (12.6)	119 (14.3)
12-15	389 (34.3)	589 (36.8)	129 (40.7)	333 (40.0)
≥16	232 (20.4)	407 (25.4)	94 (29.6)	261 (31.3)
Unknown	14 (1.2)	10 (0.6)	4 (1.3)	5 (0.6)
Cigarette smoking (lifetime pack-yr)				
Never	183 (16.1)	533 (33.3)	149 (47.0)	574 (68.9)
<25	239 (21.0)	352 (22.0)	56 (17.7)	112 (13.5)
25-50	307 (27.1)	351 (21.9)	63 (19.8)	96 (11.3)
>50	404 (35.6)	365 (22.8)	49 (15.5)	52 (6.2)
Unknown	2 (0.2)			
Frequency for strenuous or moderate exercise				
≥1/day	167 (14.7)	281 (17.6)	64 (20.2)	160 (19.2)
2-6/week	242 (21.3)	402 (25.1)	102 (32.2)	249 (29.9)
1-4/month	168 (14.8)	216 (13.5)	50 (15.8)	132 (15.9)
<1/month	472 (41.6)	553 (34.5)	86 (27.1)	179 (21.5)
Unknown	86 (7.6)	149 (9.3)	15 (4.7)	113 (13.6)
Duration of living at chlorinated-surface-water areas				
0	713 (62.8)	1,063 (66.4)	196 (61.8)	509 (61.1)
1-19	257 (22.6)	351 (21.9)	86 (27.1)	197 (23.7)
20-39	90 (7.9)	103 (6.4)	17 (5.4)	65 (7.8)
≥40	75 (6.6)	84 (5.3)	18 (5.7)	62 (7.4)
First-degree relatives with bladder cancer				
No	1,026 (90.4)	1,502 (93.8)	288 (90.9)	783 (94.0)
Yes	37 (3.3)	16 (1.0)	15 (4.7)	17 (2.0)
Unknown	72 (6.3)	83 (5.2)	14 (4.4)	33 (4.0)

motor vehicle operators, and material-moving-equipment operators.

Mechanics and repairmen, especially automobile mechanics and miscellaneous mechanics and repairmen with 10 or more years of employment in these occupations, had an increased risk of bladder cancer. Precision inspectors, testers, and related workers had a significantly increased risk. A number of white-collar workers also experienced increased risk, including real estate agents and managers; management and public relations employees; executive or legislative employees; and managers and supervisors for marketing, advertising, and sales occupations.

Table 3 presents associations for men employed in a priori industries

and occupations where the CI included 1.0. Employment in several industries previously associated with the risk of bladder cancer was also found to have an increased risk in this study. Industries or occupations with a higher risk for the longer-duration category included tire and inner-tube production; transportation services; furniture and home-furnishing stores; barber shops; machinery maintenance occupations; plumbers, pipefitters, and steamfitters; machine setup operators; drivers; operators at garage and service stations; and supervisors for motorized-equipment operators.

Table 4 presents the risk for women in industries and occupations where ORs for bladder cancer were ≥2.0 either overall or in one of the

duration categories. Few significant associations were observed. However, we did find significant elevations of risk among secondary school teachers and record clerks. Working as housekeepers or butlers or in laundering and dry cleaning was associated with a nonsignificantly increased risk. About 30% of the cases (96 of 317) and an equal proportion of controls (248 of 833) were reported to be housewives (OR = 1.0; 95% CI, 0.8 to 1.4; data not shown).

Discussion

In this population-based, case-control study of bladder cancer among men and women, we observed several statistically significant associations between certain industries and occupations and bladder

TABLE 2

Statistically Significant Associations for Bladder Cancer by Industry or Occupation for Men

Industry	All		<10 Years		≥10 Years	
	Ca/Co	OR* (95% CI)	Ca/Co	OR* (95% CI)	Ca/Co	OR* (95% CI)
Industry (SIC code)						
Plumbing, heating, and air conditioning (1711)	15/10	2.2 (1.0–5.0)	3/1	4.6 (0.5–45.1)	12/9	1.9 (0.8–4.7)
Rubber and miscellaneous plastics products (30)	12/6	3.1 (1.2–8.5)	1/1	2.0 (0.1–32.5)	11/5	3.3 (1.1–9.9)
Railroad transportation (40)	33/33	1.4 (0.8–2.3)	4/9	0.6 (0.2–2.0)	29/24	1.7 (1.0–3.1)
Motor vehicles, parts, and supplies (501)	11/3	4.5 (1.2–16.5)	5/0		6/3	2.3 (0.6–9.5)
General merchandise stores (53)	12/7	2.7 (1.0–7.1)	4/2	3.2 (0.6–18.8)	8/5	2.4 (0.7–7.9)
Automotive dealers and service station (55)	54/43	1.6 (1.0–2.4)	15/14	1.4 (0.7–3.0)	39/29	1.7 (1.0–2.7)
Real estate agents and managers (6531)	9/4	4.0 (1.2–13.5)	4/2	3.9 (0.7–23.0)	5/2	4.0 (0.7–21.6)
General automotive repair shops (7538)	20/9	3.0 (1.3–6.7)	4/3	2.0 (0.4–9.3)	16/6	3.4 (1.3–9.0)
Management and public relations (874)	6/1	9.4 (1.1–80.0)	0/0		6/1	9.4 (1.1–80.0)
Executive, legislative, and general (91)	43/39	1.6 (1.0–2.5)	13/12	1.5 (0.7–3.3)	30/27	1.6 (0.9–2.8)
Occupation (SOC code)						
Officials and administrators, public administration (11)	15/12	2.0 (0.9–4.4)	6/6	1.3 (0.4–4.2)	9/6	2.8 (1.0–8.3)
Managers: marketing, advertising, and public relations (125)	10/5	3.3 (1.1–10.0)	3/2	2.2 (0.3–14.0)	7/3	4.0 (1.0–16.3)
Purchasing agents and buyers, farm products (1443)	10/4	3.7 (1.1–12.5)	3/1	5.2 (0.4–64.7)	7/3	3.3 (0.8–13.1)
Mechanics and repairers (61)	118/118	1.3 (1.0–1.8)	21/25	1.2 (0.6–2.1)	97/93	1.4 (1.0–1.9)
Automobile mechanics (6111)	44/35	1.6 (1.0–2.6)	8/8	1.4 (0.5–3.7)	36/27	1.7 (1.0–2.8)
Miscellaneous mechanics and repairers (617)	32/25	1.8 (1.0–3.1)	8/11	1.0 (0.4–2.7)	24/14	2.4 (1.2–4.7)
Painters (construction and maintenance) (6442)	11/6	2.7 (1.0–7.7)	5/0		6/6	1.4 (0.4–4.7)
Precision inspectors, testers, and graders (6881)	6/1	10.3 (1.2–87.4)	0/0		6/1	10.6 (1.2–90.1)
Metal- and plastic-working machine operators (751, 752)	34/23	2.0 (1.1–3.4)	7/9	0.9 (0.3–2.4)	27/14	2.8 (1.4–5.4)
Supervisors: transportation and material moving (81)	11/2	6.5 (1.4–29.9)	1/0		10/2	6.0 (1.3–28.2)
Material-moving-equipment operators (831)	26/17	1.9 (1.0–3.6)	6/4	1.9 (0.5–7.3)	20/13	1.9 (0.9–3.9)
Graders, dozers, and scraper operators (8317)	8/3	4.1 (1.1–16.2)	4/1	6.9 (0.7–65.8)	4/2	2.8 (0.5–16.1)

Ca, cases; Co, controls.

* Adjusted for age, lifetime pack-years of cigarette smoking, and first-degree relative with bladder cancer.

cancer risk. These include several that had been previously noted as well as some new observations. Our major findings are summarized and discussed below.

We found a significantly increased risk of bladder cancer among those working in industries producing rubber and plastic products. A nonsignificantly increased risk was also observed in industries producing tires and inner tubes. Epidemiological studies conducted in various countries, including the United States, suggest that workers employed in rubber-related manufacturing industries have an elevated risk of bladder cancer.^{3–5} Employment in rubber-related industries is considered to have sufficient evidence for carcinogenicity to humans, particularly for the human urinary bladder.¹⁵ Exposure to aromatic amines is a suggested cause for the increased risk of bladder cancer.¹⁵ In earlier years, some countries used antioxi-

dants containing 2-naphthylamine in rubber and electric-cable manufacturing industries. In the United States, there was little exposure to 2-naphthylamine in the rubber industry. However, workers in the United States may be exposed to another antioxidant, phenyl- β -naphthylamine, which can be metabolized to 2-naphthylamine.^{5,15}

We also found an increased risk of bladder cancer among motor vehicle operators, motorized-equipment operators, drivers, and garage and service station-related occupations. These results are consistent with observations from most previous studies suggesting that truck, bus, and locomotive drivers had an increased risk of bladder cancer.^{6,16} Jobs associated with exposure to diesel or traffic fumes and polycyclic aromatic hydrocarbons are linked to an increased risk of bladder cancer in recent studies.^{17,18} A recent population-based, case-cohort study from

the Netherlands also reported that men in the highest tertiles of occupational exposure to diesel exhaust had nonsignificantly higher age- and smoking-adjusted incident rate ratios of bladder cancer than men with no exposure.¹⁹ The increased risk for drivers may come from inhalation of motor exhaust emission particulates or from on-the-road exposure to such particulates.⁵ A potential association between polycyclic aromatic hydrocarbon exposure and bladder cancer risk is supported by experimental evidence demonstrating mutagenicity and possible carcinogenicity of motor exhaust particulates and the role of motor exhaust exposure in human bladder carcinogenesis.²⁰ Another possible explanation is the low frequency of micturition typical for truck, bus, and locomotive drivers. Such habits lead to urinary retention and a higher urine pressure, resulting in more intensive and prolonged contact between potential urine-borne

TABLE 3

Nonsignificant Bladder Cancer Risk for Iowa Men Employed in a Priori-Defined High-Risk Industry or Occupation

Industry/Occupation	All		<10 Years		≥10 Years	
	Ca/Co	OR* (95% CI)	Ca/Co	OR* (95% CI)	Ca/Co	OR* (95% CI)
Industry (SIC code)						
Painting and paperhanging (172)	9/5	2.9 (0.9–9.1)	3/0		6/5	1.9 (0.5–6.5)
Petroleum and coal products (29)	7/9	1.0 (0.4–2.9)	2/1	3.2 (0.3–40.9)	5/8	0.8 (0.2–2.6)
Petroleum refining (291)	7/8	1.1 (0.4–3.2)	2/1	3.2 (0.3–40.9)	5/7	0.8 (0.3–2.8)
Tires and inner tubes (301)	6/4	2.7 (0.7–9.6)	0/1		6/3	3.4 (0.8–14.1)
Primary metal industry (33)	19/31	0.7 (0.4–1.3)	6/4	1.8 (0.5–6.4)	13/27	0.5 (0.3–1.1)
Miscellaneous manufacturing industries (39)	6/5	1.6 (0.5–5.2)	3/2	2.2 (0.4–13.4)	3/3	1.2 (0.2–5.9)
Railroads (401)	11/8	1.5 (0.6–3.9)	3/2	2.1 (0.3–13.3)	8/6	1.4 (0.5–4.0)
Local and interurban passenger transit (41)	6/3	3.4 (0.8–14.2)	3/1	7.8 (0.8–77.2)	3/2	1.8 (0.3–10.8)
Transportation services (47)	6/3	2.8 (0.7–11.8)	2/1	2.9 (0.2–35.4)	4/2	2.7 (0.5–15.8)
Apparel and accessory stores (56)	8/6	1.8 (0.6–5.3)	3/1	3.4 (0.3–33.8)	5/5	1.4 (0.4–5.1)
Furniture and home-furnishing stores (571)	6/6	1.3 (0.4–4.2)	0/3		6/3	2.7 (0.6–11.5)
Barber shops (724)	5/3	1.8 (0.4–8.0)	0/0		5/3	1.8 (0.4–8.0)
Occupation						
Machinery maintenance occupation (614)	5/1	7.1 (0.8–65.9)	2/0		3/1	3.8 (0.3–43.7)
Plumbers, pipefitters, and steamfitters (645)	13/9	2.0 (0.8–4.9)	4/2	1.8 (0.3–10.7)	9/7	2.0 (0.7–5.7)
Machine setup operators (73, 74)	8/6	2.0 (0.7–5.9)	3/3	1.6 (0.3–8.2)	5/3	2.4 (0.5–10.5)
Metal- and plastic-working machine setup operators (731, 732)	6/3	3.2 (0.8–12.9)	3/1	5.4 (0.5–52.8)	3/2	2.1 (0.3–13.2)
Supervisors for motorized-equipment operators (811)	7/1	7.1 (0.9–58.6)	1/0		6/1	6.3 (0.7–52.6)
Drivers (8212–8215)	78/79	1.3 (0.9–1.8)	21/24	1.3 (0.7–2.4)	57/55	1.3 (0.9–2.0)
Garage and service station-related occupations (873)	27/20	1.7 (0.9–3.1)	10/8	1.8 (0.7–4.8)	17/12	1.6 (0.8–3.5)

Ca, cases; Co, controls.

* Adjusted for age, lifetime pack-years of cigarette smoking, and first-degree relative with bladder cancer.

TABLE 4

Risk (≥2.0) of Bladder Cancer by Industry and Occupation for Women (Based on Three or More Exposed Cases)

Industry/Occupation	All		<10 Years		≥10 Years	
	Ca/Co	OR* (95% CI)	Ca/Co	OR* (95% CI)	Ca/Co	OR* (95% CI)
Industry (SIC code)						
Food stores (54)	8/13	1.8 (0.7–4.5)	2/4	0.8 (0.1–4.6)	6/9	2.5 (0.8–7.3)
Grocery stores (5411)	8/10	2.4 (0.9–6.5)	2/3	1.3 (0.2–8.2)	6/7	3.1 (1.0–9.8)
Insurance carriers (63)	6/12	1.4 (0.5–3.9)	3/3	2.7 (0.5–15.4)	3/9	0.9 (0.2–3.7)
Personal services (72)	10/23	0.9 (0.4–1.9)	1/1	3.2 (0.2–55.7)	9/22	0.8 (0.3–1.8)
Occupation (SOC code)						
Accountants, auditors, and other financial specialists (141)	4/7	1.7 (0.4–6.4)	2/1	7.1 (0.6–85.0)	2/6	0.8 (0.1–4.7)
Secondary school teachers (233)	7/6	3.8 (1.2–12.1)	4/3	4.1 (0.9–19.4)	3/3	3.5 (0.7–19.3)
General office occupation (463)	6/16	0.8 (0.3–2.2)	4/4	2.7 (0.6–12.6)	2/12	0.3 (0.1–1.6)
Record clerks (469)	10/7	2.7 (1.0–7.7)	4/5	1.5 (0.4–6.2)	6/2	5.7 (1.1–30.2)
Housekeepers and butlers (505)	3/2	4.3 (0.7–28.9)	0/0		3/2	4.4 (0.7–29.0)
Laundering and dry cleaning (7658)	3/1	9.3 (0.9–94.8)	2/0		1/1	2.1 (0.1–36.9)

Ca, cases; Co, controls.

* Adjusted for age, lifetime pack-years of cigarette smoking, and first-degree relative with bladder cancer.

carcinogenic agents and the sensitive basal cells of the distended urothelium.⁶

We also observed a significantly increased risk of bladder cancer for mechanics and repairers, particularly automobile mechanics and miscellaneous mechanics and repairers; met-

al- and plastic-working machine operators; graders, dozers, and scraper operators; and handlers, equipment cleaners, and laborers. An increased risk of bladder cancer was also reported for these occupations in earlier studies.^{5,21–23} Employment as mechanics and machinists could ex-

pose one to mists from oils, solvents, or metal dusts. Mineral oils contain a variety of additives and contaminants, including polycyclic aromatic hydrocarbons, nitrosamines, chlorinated paraffins, long-chain aliphatics, sulfur, *N*-phenyl-2-naphthylamine, and formaldehyde,²⁴ with

some of these compounds having been associated with the risk of bladder cancer.⁵

Employment as a painter or printer has been associated with an increased risk of bladder cancer.^{5,22,24-26} The recent study by Zeegers et al¹⁹ also reported a non-significantly increased risk of bladder cancer among men after occupational exposure to paint components. Here, we found an increased risk of bladder cancer for painters or workers in the painting and paperhanging industries. Painters use various pigments, extenders, and solvents and therefore could be exposed to many known or suspected carcinogens in paints (such as benzidine, polychlorinated biphenyls, formaldehyde, and asbestos) and related solvents (eg, benzene, dioxane, and methylene chloride).⁵ The International Agency for Research on Cancer concluded that there is sufficient evidence for the carcinogenicity of occupational exposure as a painter.²⁷

In a case-control study of white women by Silverman et al,²⁹ involving 652 bladder cancer cases and 1266 controls, employment in rubber processing was the only industry suspected a priori that had a statistically significant increased risk of bladder cancer. We observed few significant associations among women. Worth noting was the increased risk observed for employment in laundering and dry cleaning or as housekeepers and butlers. Excess risk of bladder cancer mortality was also observed among dry-cleaning workers in cohort studies^{29,30} and case-control studies.^{21,22} An increased risk of bladder cancer was reported from earlier studies for female housekeepers and butlers³¹ and janitors.⁶ Workers in these industries or occupations may come into close contact with various solvents.

Several studies have reported an increased risk of bladder cancer among plumbers.^{21,22,32} In our study, we also observed a significantly increased risk of bladder cancer (OR = 2.2; 95% CI, 1.0 to 5.0) for workers

in the plumbing, heating, and air conditioning industries. Plumbers and pipefitters encounter many hazardous materials, among them asbestos, metal fumes, and gases from welding, brazing, and soldering and solvents used to join plastic pipe.

Caution should be exercised in interpreting our study results. First, although our study is relatively large, several observations were based on relatively small numbers; therefore, chance cannot be ruled out as an explanation for many of the observed associations. Second, because many comparisons were made, some significant associations would be expected by chance alone. Several other potential limitations may also hamper the interpretation of our study findings. Occupational and industrial categories are but crude surrogates for potentially carcinogenic exposures. It is likely that a wide range of exposure intensity and types of exposure occurred within individual categories, introducing exposure misclassification. Such misclassification was probably nondifferential among cases and controls and therefore would be expected to attenuate the strength of estimated risks. Information regarding lifetime job history depended on subject recall, rather than data collected from industry records. However, other studies have shown good agreement between work history job titles reported by study subjects or next-of-kin and industry personnel records.³³⁻³⁷ The fact that our major findings are consistent with many other studies regarding the association between bladder cancer risk and rubber, transportation, and painting industries can be regarded as a validation of our results.

Selection bias is an unlikely explanation for the observed association between various occupations and industries and bladder cancer risk in our study. As we discuss elsewhere,⁸ the population-based controls were randomly selected from the general population of Iowa by using driver's license listings and rosters of the US

Health Care Financing Administration. The population distribution of individuals aged 40 to 64 years with drivers' licenses in Iowa parallels census enumeration data with respect to county of residence, 5-year age groups, urbanicity, and sex, suggesting an unbiased sampling framework.³⁸ US Health Care Financing Administration listings provide an estimated 98% coverage of the US population older than age 64, and this source has been used successfully in selecting controls elsewhere.³⁹

On the other hand, certain characteristics of this study strengthen the interpretation of our findings. In this population-based, case-control study, cases were histologically confirmed incident bladder cancer patients, and information regarding lifetime job-exposure history and other potential risk factors was collected from study subjects or their next of kin, rather than relying on death certificates or tumor registry records. The relatively high response rates from both cases and controls also lend confidence to study findings.

In conclusion, in this population-based, case-control study, we found an increased risk of bladder cancer for the rubber and plastics, transportation, and painting industries. These observations are consistent with a majority of previous findings. A significantly increased risk of bladder cancer was also observed for mechanics and for metal- and plastic-working machine operators. Several industries or occupations also showed a nonsignificantly increased risk of bladder cancer, which have been inconsistently associated with the risk of bladder cancer in earlier studies. These include mechanics and machinery operators, barbers, plumbers and pipefitters, housekeepers, and those working in laundering and dry cleaning. While chance cannot be ruled out as a possible explanation, these associations warrant further investigation.

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