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High bladder cancer mortality in rural New England (United States): an etiologic study

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An interview study of next-of-kin of 325 persons who died of bladder cancer and 673 individuals who died of other causes in Vermont and New Hampshire (United States) was conducted to assess reasons for the persistent pattern of elevated bladder cancer mortality for both genders in rural New England. There was some evidence of elevated risks for both leather and textile workers that rose to over twofold for workers who also lived near these industries and for persons with French-Canadian ancestry. Occupational exposures in the textile and leather industry may explain at least a portion of the excess bladder cancer risk in rural New England. *Cancer Causes and Control* 1995, **6,** 361-368

Key words: Bladder neoplasm, case-control study, etiology, leather industry, textile industry, occupational exposure, United States.

Introduction

A striking feature of the United States cancer-mortality maps of 1950-69[1] (Figure 1) is the clustering of high rates of bladder cancer in rural New England for men and women. Women in this area experienced the highest bladder-cancer mortality rates in the US, whereas the rates for men in rural New England and adjoining areas of New York State were second only to New Jersey. In contrast to New Jersey, where concentration of the chemical industry may contribute to the excess risk, the reasons for the high rates in rural New England are unclear.[2,3]

Updated cancer maps by the US National Cancer Institute have revealed persistence of the excess bladder cancer rates in this region for the period 1970-89 (Figure 2). To evaluate possible risk factors prevalent in this area such as French-Canadian ancestry, consumption of French-Canadian foods and fiddlehead or bracken fern (a known animal carcinogen),[4] occupational exposures, and residence near leather, textile, or paper/pulp factories, we analyzed data from a case-control study of bladder cancer conducted in Vermont and New Hampshire.

Materials and methods

The study included all White residents of Vermont and New Hampshire who died during 1975-79 from bladder cancer (ICD-8[5] code 188; ICD-9[6] code 188.0-188.9), identified from the Vital Records and Health Statistics Office of New Hampshire and the Public Health Statistics Office of Vermont. Two controls per case, matched on state, gender, race, age (± 2 years), and year of death, were selected randomly from all other resident deaths (excluding suicides). One of the two controls per subject was matched also on county of residence. A mortality-based study design was used because no population-based cancer registries covered the region at

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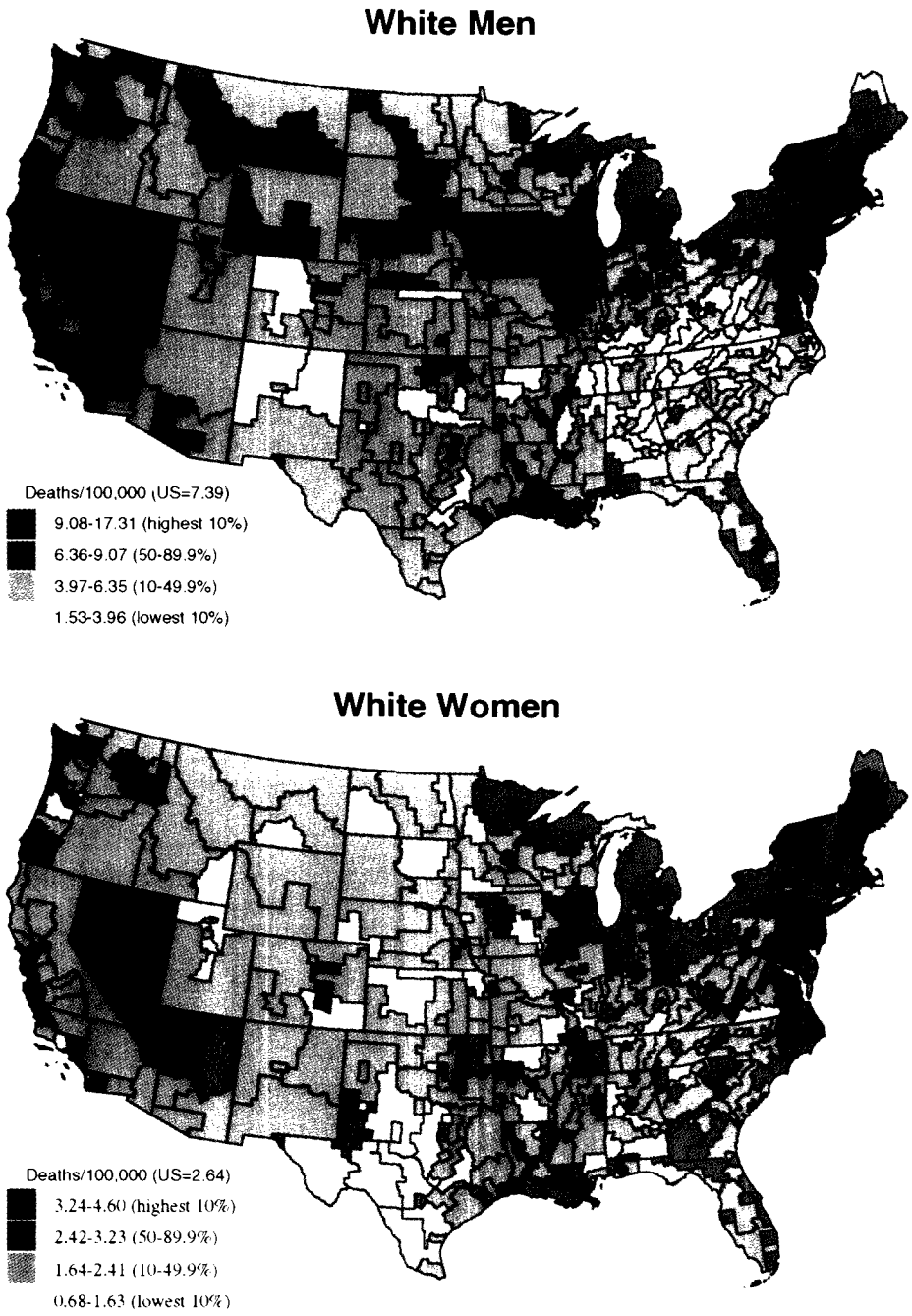

Figure 1. Bladder cancer mortality rates by state economic area for White men and women (1950-69).

that time, making the logistics of prospectively identifying incident cases prohibitive. Details of subject selection procedures are presented elsewhere.[3]

During the time period 1975-79, there were 440 White residents of Vermont and New Hampshire who died of bladder cancer. Interviews were completed for the next-of-kin of 224 males and 101 females (74 percent). A total of 923 White controls were selected and the next-of-kin of 73 percent were interviewed (459 males, 214 females). Refusal was the most common reason for nonresponse for proxies of both cases and controls. However, decedents for whom proxy interviews were obtained were similar to decedents without proxy interviews with respect to case-control status, gender, age, and county of residence.

Questionnaires sought information on demographic characteristics, lifetime occupational and residential histories, history of tobacco and beverage use,

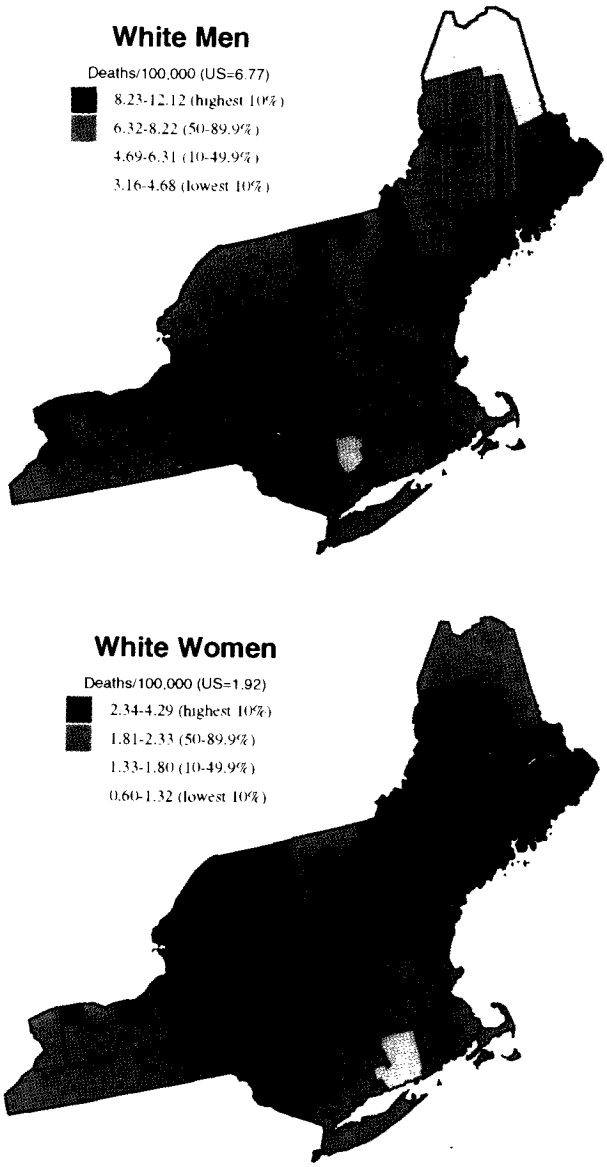

Figure 2. Bladder cancer mortality rates by state economic area for White men and women (1970-89); Connecticut, Maine, Massachusetts, New Hampshire, New York, Rhode Island, and Vermont.

consumption of selected dietary items including bracken fern, and medical history including badder infection. For each job held for one year or longer since age 12, the name of the employer, job title, duties, and years worked were collected and coded using the SIC[7] and SOC[8] systems. Occupational and industrial categories were formed based on these codes and a check list of 31 occupations and industries of interest. Only those categories for each gender reported by five or more cases or controls are included in this report.

Both conditional and unconditional logistic regression[9,10] were used to calculate odds ratios (OR) for the variables of interest. Since both methods yielded similar results, analyses are presented for the unconditional approach because it allowed the inclusion of data from all subjects. Separate analysis for the two control series also yielded similar results, so only the analysis for the combined control series is presented. The variables for residence (Vermont, New Hampshire), age (< 65, 65-74, 75-84, > 84), and history of bladder infection (yes, no) were included in models to adjust for potential confounding. Age-adjusted population-attributable risk (PAR) estimates of the proportion of bladder cancer due to employment in textiles and/or leather industries were calculated separately for men and women by using the method of Whittemore.[11,12]

Results

Table 1 presents ORs for bladder cancer for known or suspected risk factors. Since the risk estimates were similar for men and women, the combined results are presented. History of bladder infection at least five years prior to death (OR = 3.7, 95 percent confidence interval [CI] = 2.5-5.4) and French-Canadian ancestry (OR = 1.3, CI = 1.0-1.8) were associated with statistically significant excess risk. However, there were no significant elevations in risk for consumption of traditional French-Canadian foods such as pig's feet (*ragout de patte de cochon*), pork pies or other meat pies (*tourtieres*), or salmon pie (*tarte au saumon*). Risk was not affected by consumption of bracken fern, type of water supply used (*i.e.*, community or well), or by consumption of coffee, including heavy consumption of greater than 21 drinks per week (OR = 1.0, CI = 0.6-1.7). Risks associated with cigarette smoking were not elevated for ever-smokers (OR = 1.0, CI = 0.7-1.4) and only slightly elevated for heavy smokers of 40 or more cigarettes per day (OR = 1.2, CI = 0.7-1.8). When the smoking-related causes of death (*e.g.*, cancers of the buccal cavity, pharynx, esophagus, pancreas, and respiratory system; ischemic heart disease; pulmonary heart disease; symptomatic heart disease; cerebrovascular disease; bronchitis, emphysema, and other diseases of the respiratory system) were excluded from the control series, risk due to smoking rose slightly to 1.2 (CI = 0.8-1.7).

The ORs for employment in selected industries or occupations among men are shown in Table 2. Risks were elevated nonsignificantly for men ever employed in the leather, textile, or lumber industry; elevated nonsignificantly for men employed for more than five years in the leather or lumber industry; and elevated significantly for men employed for more than five years in the textile industry (OR = 2.2, CI = 1.2-3.7). The age-adjusted PAR for employment in the textile and/or

Table 1. Risk of bladder cancer for known or suspected risk factors among White men and women in New Hampshire and Vermont

Factor	Cases (n = 325)	Controls (n = 673)	Adjusted	
			OR[a]	(CI)[b]
History of bladder infection	79 (24.3)	57 (8.5)	3.7	(2.5-5.4)
French-Canadian ancestry	78 (24.0)	137 (20.4)	1.3	(1.0-1.8)
Ever ate bracken fern	24 (7.4)	71 (10.6)	0.6	(0.4-1.0)
Regularly ate bracken fern	15 (4.6)	38 (5.6)	0.8	(0.4-1.4)
Ever used community water	294 (90.5)	604 (89.8)	1.1	(0.7-1.8)
Ever used well water	215 (63.1)	441 (65.5)	1.0	(0.7-1.3)
Ever drank coffee	293 (90.2)	606 (90.0)	0.9	(0.6-1.5)
Ever smoked cigarettes	196 (60.3)	409 (60.8)	1.0	(0.7-1.4)

[a] All ORs are relative to risk for subjects who were never exposed to that factor. Except for history of bladder infection which was adjusted for age and state, all ORs are adjusted for age, state, and history of bladder infection in a logistic analysis. Percentages are in parentheses.
[b] CI = 95% confidence interval.

leather industry was 6.5 percent (CI = −1.6%-14.6%). Although based on small numbers, ORs were elevated significantly for men employed in the auto industry, including those ever employed (OR = 3.5, CI = 1.1-11.0) and those employed for more than five years (four exposed cases, zero controls). Risks also were elevated significantly for men employed for more than five years as truck drivers (OR = 2.4, CI = 1.2-4.8).

Among women, bladder cancer was not elevated significantly in any occupation or industry (Table 3).

Table 2. Risk of bladder cancer associated with employment in selected industries or occupations among White men in New Hampshire and Vermont (224 cases, 459 controls)

	Ever worked				Worked more than 5 years			
	Cases	Controls	Adjusted		Cases	Controls	Adjusted	
			OR[a]	(CI)[b]			OR[a]	(CI)[b]
Industry								
Leather	27 (12.1)	38 (8.3)	1.5	(0.9-2.6)	11 (4.9)	18 (3.9)	1.4	(0.6-3.2)
Textile	40 (17.9)	61(13.3)	1.4	(0.9-2.2)	29 (13.0)	32 (7.0)	2.2	(1.2-3.7)
Paper/pulp	14 (6.2)	36 (7.8)	0.8	(0.4-1.6)	7 (3.1)	20 (4.4)	0.7	(0.3-1.6)
Lumber	39 (17.4)	65 (14.2)	1.4	(0.9-2.2)	22 (9.8)	34 (7.4)	1.5	(0.8-2.6)
Printing	13 (5.8)	30 (6.5)	0.9	(0.4-1.7)	6 (2.7)	17 (3.7)	0.8	(0.3-2.0)
Dairy farming	35 (15.6)	81 (17.6)	0.8	(0.5-1.3)	22 (9.8)	58 (12.6)	0.8	(0.5-1.4)
Other farming	38 (17.0)	105 (22.9)	0.7	(0.4-1.0)	21 (9.4)	67 (14.6)	0.6	(0.3-1.0)
Construction	52 (23.2)	119 (25.9)	0.9	(0.6-1.3)	23 (10.3)	67 (14.6)	0.6	(0.4-1.1)
Asphalt	12 (5.4)	39 (8.5)	0.6	(0.3-1.3)	4 (1.8)	12 (2.6)	0.7	(0.2-2.3)
Auto industry	9 (4.0)	5 (1.1)	3.5	(1.1-11.0)	4 (1.8)	0 (0.0)	∞	—
Shipbuilding	16 (7.1)	37 (8.1)	1.1	(0.6-2.0)	7 (3.1)	17 (3.7)	1.0	(0.4-2.5)
Occupation								
Painter	5 (2.2)	12 (2.6)	0.9	(0.3-2.7)	1 (0.4)	3 (0.6)	0.6	(0.06-6.6)
Electrician	8 (3.6)	10 (2.2)	1.5	(0.5-4.0)	5 (2.2)	6 (1.3)	1.7	(0.5-5.9)
Carpenter	19 (8.5)	39 (8.5)	1.0	(0.6-1.8)	10 (4.5)	27 (5.9)	0.7	(0.3-1.6)
Truck driver	32 (14.3)	53 (11.6)	1.4	(0.8-2.2)	19 (8.5)	18 (3.9)	2.4	(1.2-4.8)

[a] All ORs are relative to risk for subjects who were never employed in that industry or occupation. The ORs are adjusted for age, state, and history of bladder infection in a logistic analysis. Percentages are in parentheses.
[b] CI = 95% confidence interval.

Table 3. Risk of bladder cancer associated with employment in selected industries among White women in New Hampshire and Vermont (101 cases; 214 controls)

Industry	Ever worked				Worked more than 5 years			
	Cases	Controls	Adjusted		Cases	Controls	Adjusted	
			OR[a]	(CI)[b]			OR[a]	(CI)[b]
Leather	8 (7.9)	18 (8.4)	1.1	(0.4-2.8)	3 (3.0)	10 (4.7)	0.7	(0.2-2.9)
Textile	33 (32.7)	63 (29.4)	1.2	(0.7-2.0)	14 (13.9)	31 (14.5)	1.2	(0.6-2.5)
Paper/pulp	3 (3.0)	6 (2.8)	1.2	(0.3-5.2)	1 (1.0)	2 (0.9)	0.7	(0.1-8.4)
Lumber	1 (1.0)	8 (3.7)	0.2	(0.03-2.1)	0 (0.0)	1 (0.5)	0	—
Printing	1 (1.0)	5 (2.3)	0.3	(0.04-3.3)	0 (0.0)	3 (1.4)	0	—
Dairy farming	4 (4.0)	9 (4.2)	0.5	(0.1-2.0)	2 (2.0)	6 (2.8)	0.5	(0.9-2.8)
Other farming	9 (8.9)	11 (5.1)	1.8	(0.7-4.9)	7 (6.9)	7 (3.3)	2.5	(0.8-8.1)

[a] All ORs are relative to risk for subjects who were never employed in that industry. The ORs are adjusted for age, state, and history of bladder infection in a logistic analysis. Percentages are in parentheses.
[b] CI = 95% confidence interval.

Slight, nonsignificant elevations were observed for employment in the leather, textile, and paper and pulp industries and for farming other than dairy farming. The age-adjusted PAR for employment in the textile industry was 4.4 percent (CI = −11.3%-20.1%). The OR increased further among women employed for more than five years in farming other than dairy, but the ORs decreased or stayed the same for longer duration of employment in the other industries.

Table 4 presents ORs associated with working at or living near a leather, textile, or paper/pulp factory. Significantly elevated risks of greater than 2.0 were seen for men who both worked at and lived one mile or less from a leather or textile factory. Similar associations were seen for women, but the ORs were not significant. Little or no risk was seen for subjects who worked at a leather or textile factory but did not live near the plant, and *vice versa*. Small nonsignificant excesses were seen

Table 4. Risk of bladder cancer associated with employment at and/or residence within one mile of selected types of industries among White men and women in New Hampshire and Vermont

Industry	Worked at	Lived near	Men				Women			
			Cases	Controls	Adjusted		Cases	Controls	Adjusted	
					OR[a]	(CI)[b]			OR[a]	(CI)[b]
Leather	No	No	182	388	1.0	—	84	182	1.0	—
	Yes	No	15	26	1.1	(0.5-2.2)	3	11	0.8	(0.2-3.0)
	No	Yes	15	30	1.1	(0.6-2.2)	7	14	0.9	(0.3-2.5)
	Yes	Yes	12	12	2.6	(1.1-6.1)	5	7	1.7	(0.5-6.0)
Textile	No	No	161	354	1.0	—	62	138	1.0	—
	Yes	No	23	43	1.2	(0.7-2.1)	19	42	1.0	(0.5-1.9)
	No	Yes	22	43	1.1	(0.6-2.0)	6	13	0.9	(0.3-2.7)
	Yes	Yes	17	18	2.4	(1.2-4.8)	14	18	2.0	(0.9-4.6)
Paper/pulp	No	No	202	406	1.0	—	91	197	1.0	—
	Yes	No	6	20	0.6	(0.2-1.5)	2	5	1.1	(0.2-6.0)
	No	Yes	7	15	0.9	(0.4-2.4)	7	11	1.4	(0.5-3.9)
	Yes	Yes	8	15	1.2	(0.5-3.0)	1	1	1.7	(0.1-33.7)

[a] All ORs are relative to risk for subjects who were never employed in each occupation and who never lived one mile or less from each type of factory. The ORs are adjusted for age, state, and history of bladder infection in a logistic analysis.
[b] CI = 95% confidence interval.

for women working at and/or living near a paper/pulp facility; but among men, an excess risk was observed only for the combination of occupational and residential paper/pulp exposure.

Discussion

Mapping cancer mortality at the county level has been useful in generating etiologic clues and targeting epidemiologic research.[13,14] For example, high rates of lung cancer mortality observed among men along the southeastern US Atlantic coast were found in case-control studies to be associated with asbestos exposures in shipbuilding, particularly during World War II.[15-17] High rates of oral cancer among women in rural counties of the South were found to be related to the long-standing use of smokeless tobacco.[18]

Bladder cancer shows considerable geographic variation, especially among men, with elevated rates in urban areas of the northeastern and upper midwestern US. Occupational factors appear to contribute to the high rates in areas such as New Jersey, where the chemical industry is concentrated and workers have been exposed to aromatic amines that are carcinogenic to the bladder.[2,19]

In an attempt to explain the persistent geographic clustering of bladder cancer in rural New England, we analyzed data from a case-control study of bladder cancer conducted in Vermont and New Hampshire.[3] Analyses focused on several industries prevalent in the region that may involve exposure to bladder carcinogens. Of particular interest is the textile industry which used dyes that have been linked to bladder cancer.[19] It once employed substantial numbers of New England men and women both in factories and in their homes as 'cottage industries'.[20] We found a nonsignificant excess risk for men ever employed in the textile industry and a significant excess risk for men employed more than five years. However, the association was weaker among women, whose exposure to industrial chemicals may have been generally lower due to specific job practices. When the textile industry left New England during the 1920s and 1930s, it moved to the southern US. The National Bladder Cancer Study, which included subjects from Atlanta (Georgia), did not reveal any positive associations with the textile industry,[21] but the differences in risk may reflect regional differences in exposure. In New England, the textile industry produced primarily wool with some cotton, while in the South, it produced cotton, polyester, nylon, and acrylics, but no wool. The chemicals used to degrease, scour, bleach, and dye vary for each fiber type and may explain the regional variation in bladder cancer risk.

The leather industry was also once concentrated in New England,[20] and thus evaluated as a possible cause for the high rates of bladder cancer in both genders. In previous studies, elevated risks have been reported for leather workers exposed to leather dust, dyes, and solvents.[19] In our study, overall risks were elevated for men, but did not increase with duration of employment. Since risks were elevated only slightly for women in leather occupations, the evidence is less persuasive that this exposure explains the high rates of bladder cancer among women in rural New England. However, these lower than anticipated risks may be due to misclassification of occupational exposures by their next-of-kin.

The paper and pulp industry has not been linked previously with bladder cancer, but it is heavily concentrated in New England and a source of air and water pollutants that may be carcinogenic.[22] We observed no significant association between bladder cancer risk and employment in this industry for either gender.

Risks were elevated significantly for long-term employment as a truck driver, although detailed analyses reported elsewhere[3] could not determine whether the excess risk was due to diesel emissions or some other factor associated with this occupation. Truck driving also has been associated with excess risk of bladder cancer in the National Bladder Cancer Study,[23] but it seems unlikely to contribute to the regional excess seen among men, nor can it explain the high rates among women.

We also evaluated other potential risk factors prevalent to this area such as French-Canadian ancestry and dietary habits including consumption of French-Canadian foods and bracken fern (fiddlehead). We observed slight, nonsignificant elevations in both men and women associated with French-Canadian ancestry, but risks were not elevated for consumption of various traditional French-Canadian foods. Bracken fern has been shown to be carcinogenic in experimental and observational animal studies, producing bladder tumors in rats, guinea pigs, and cattle.[4] Our study revealed no consistent association between consumption of bracken fern used mainly as a condiment in salads and risk of bladder cancer.

Cigarette smoking is an established cause of bladder cancer, with smokers generally having two to three times the risk of nonsmokers.[19] Our study revealed no significant elevations in risk, however, even when controls with smoking-related causes of death were excluded. This lack of a significant association with smoking is not surprising since it has been demonstrated[24] that the use of dead controls, even when smoking-related causes of death have been excluded, likely will lead to a biased underestimate of risk. Like

most other studies of bladder cancer,[19] we found a positive association with bladder infection, and no association with coffee drinking.

There are several limitations to this study that should be considered. First, it was based on death certificates; thus, all information was obtained from proxy respondents. Most studies indicate that proxy respondents tend to underestimate exposures such as the number of jobs and residences held, as well as medical conditions, although overreporting also can occur.[25] Lack of knowledge or difficulty in recall by the proxy also may have influenced the responses, including those for the dietary variables where the effects of misclassification could have masked small increases in risk.[25] In addition, there may have been differential misclassification of exposure by next-of-kin of controls who died of conditions other than cancer,[25] even though questions were asked in a similar manner to all subjects by trained interviewers. Second, the control group was representative of people from the general population who had died; thus, controls probably had an overrepresentation of risk factors (*e.g.*, smoking and drinking) that contribute to mortality compared with the general population. Third, the number of subjects, especially women, reporting exposure to any specific occupation or industry was small.

Nevertheless, this case-control study did find elevated bladder cancer risks associated with textile and leather work, two industries for which there was *a priori* suspicion that they might be involved. If these risks are causal, then based on the estimates of relative risk and percent of the population exposed from this investigation, approximately seven percent of bladder cancer mortality among males and four percent among females residing in these two states could be attributable to work in these industries. Nationally, little of bladder cancer mortality can be attributed to work in these industries since only three percent of male controls and four percent of female controls from a large, national, population-based study[20,26] reported such an occupational history (compared with 19 percent of men and 29 percent of women in the current study). Thus, the excess risks attributable to these two industries in Vermont and New Hampshire may account for about one-third of the excess mortality from bladder cancer in these two states compared with that in the total US for the period 1970-89. Again, if these exposures are indeed causal, the actual proportion of the excess risks explained is likely to be higher than one-third since the biases involved in next-of-kin interviews would tend to underestimate both the risks and the proportions exposed. Even so, the substantial excess risks unexplained by these two industries, along with the continually high bladder-cancer mortality rate in these two states despite the departure of these industries from the region decades ago, argue in favor of other, as yet unidentified factors contributing to the excess rates of bladder cancer in rural New England.

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