

Epidemiological Characteristics of Squamous Cell Carcinoma and Adenocarcinoma of the Bladder¹

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ABSTRACT

Recent incidence data from the United States indicate that transitional cell carcinoma accounts for the vast majority (95%) of bladder tumors in this country, with squamous cell carcinoma (less than 3%) and adenocarcinoma (less than 2%) comprising nearly all the remaining cases. Rates of squamous cell carcinoma and adenocarcinoma were higher in blacks compared to whites, while the reverse was true for transitional cell carcinoma. All three tumors predominated in males, especially transitional cell carcinoma. A population-based case-control study of bladder cancer conducted in 10 geographical areas of the United States identified 43 patients with squamous cell carcinoma and 32 with adenocarcinoma to permit an examination of risk factors. Cigarette smoking was significantly associated with risk of squamous cell carcinoma, with the relative risk rising to 6.1 among smokers of 40 or more cigarettes/day. Significantly elevated risks of squamous cell carcinoma were also associated with a history of 3 or more urinary tract infections (relative risk = 5.7) and with employment as welders and cooks. Risk factors were generally less conspicuous for adenocarcinoma, except for a significant trend with the amount of coffee drinking; however, this finding is based on small numbers and should be interpreted cautiously.

INTRODUCTION

During 1973-1977 in the United States, cancer of the urinary bladder accounted for 6.7% of all newly diagnosed cancers in men and 2.4% in women (1). Most bladder cancers were transitional cell carcinomas (95.1%), with small proportions of squamous cell carcinoma (2.7%) and adenocarcinoma (1.6%). Epidemiological studies have identified several risk factors for bladder cancer, including cigarette smoking (2) and occupational exposures to aromatic amines (3). Coffee drinking has not been consistently related to bladder cancer risk (4), and artificial sweeteners play little if any role (5). However, epidemiological studies of the uncommon histological types of bladder cancer have not appeared in the literature due to their rarity, with the exception of squamous cell carcinomas that may complicate severe longstanding cystitis (6, 7), notably cases of schistosomiasis haematobium in endemic regions (8).

In a large population-based case-control study of bladder carcinoma which was designed to assess the influence of artificial sweeteners and other suspected risk factors, we routinely obtained data on histological diagnosis. The identification of 43 patients with squamous cell carcinoma and 32 with adenocarcinoma thus provided a unique opportunity for an initial evaluation of their epidemiological characteristics.

MATERIALS AND METHODS

The Surveillance, Epidemiology, and End Results Program of the National Cancer Institute has documented since 1973 all newly diag-

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nosed cases of cancer in selected states and metropolitan areas covering approximately 10% of the United States population. Through the SEER³ program and the New Jersey Cancer Registry, we identified all residents of metropolitan Atlanta, Detroit, New Orleans, San Francisco, and Seattle and the states of Connecticut, Iowa, New Mexico, Utah, and New Jersey, age 21-84 years, who were newly diagnosed with histologically proven carcinoma of the urinary bladder during a 1-year period beginning in December 1977. Details of the study and methods have been presented elsewhere (5, 9). During the study period, 4045 eligible cases were identified and contacted for interview within 90 days of diagnosis; 3763 cases were alive at the time of contact and 2982 agreed to be interviewed. Information on the histological type of bladder carcinoma was available from hospital records for 2915 interviewed cases; 2834 were transitional cell carcinoma, 43 were squamous cell carcinoma, and 32 were adenocarcinoma. Six patients with undifferentiated or anaplastic carcinoma were excluded from the analyses presented here.

Controls comprised an age- and sex-stratified random sample of the general population in the 10 geographic areas, an approximately 2:1 frequency-matching ratio of controls to cases being used. Controls age 21-64 years were chosen from a census of individuals obtained through a random-digit dialing procedure, in which telephone numbers were randomly selected from all residential telephones in each area (98% of all cases also had telephones). Controls age 65-84 years were randomly selected from the enumeration of United States citizens over age 65 years obtained by the Health Care Financing Administration. Of the controls thus selected, 83% agreed to participate (5782 controls).

Structured questionnaires were administered through personal interviews conducted in the homes of respondents by trained interviewers. Data from lifetime histories of tobacco use, urinary tract infection, occupation, coffee drinking, artificial sweeteners, and diabetes mellitus were evaluated by histological type of carcinoma. Results for all cases combined have been presented elsewhere for artificial sweeteners (5), coffee drinking (4), cigarette smoking (10), and urinary tract infection (11). Occupational analysis was based upon a *posteriori* examination of work histories for all cases. Occupations reported by 3 or more cases were examined further and those associated with statistically significantly increased risks are presented. Due to the nature of this analysis and small numbers, results should be interpreted with caution.

The measure of association used is the maximum likelihood estimate of the relative risk. Potentially confounding variables were controlled through multiple contingency table analysis with 95% CI values for individual risk estimates calculated according to the method of Gart (12). Relative risk estimates for squamous cell carcinoma and adenocarcinoma were adjusted for sex and age (adjustment for race did not alter risk estimates). The Mantel extension of the Mantel-Haenszel test (2-tailed) was used to test for linear trend (13).

RESULTS

United States Incidence Data. Incidence data routinely collected by the SEER Program during 1973-1982 permitted a breakdown of bladder cancer incidence by histological type, sex, and racial group. As shown in Table 1, the male predilection seen for transitional cell carcinoma was less prominent for squamous cell carcinoma and adenocarcinoma. Whites had higher rates of transitional cell carcinoma and lower rates of

³ The abbreviations used are: SEER, Surveillance, Epidemiology, and End Results Program of the National Cancer Institute; RR, relative risk; CI, confidence interval.

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Table 2 Relative risk estimates of squamous cell carcinoma, adenocarcinoma, and transitional cell carcinoma of the bladder by suspected bladder cancer risk factors, in 10 geographic areas of the United States

	Squamous cell carcinoma ^a (43) ^b		Adenocarcinoma ^a (32)		Transitional cell carcinoma ^c (2834)	
	RR	95% CI	RR	95% CI	RR	95% CI
Cigarette smoking ^d (cigarettes/day)						
Never smoked	1.0 ^e (11)		1.0 ^e (14)		1.0 ^e (616)	
<20	1.4 (6)	0.5-4.4	0.8 (5)	0.2-2.5	1.8 ^f (543)	1.6-2.1
20-39	3.4 ^f (16)	1.3-8.6	1.5 (11)	0.6-3.8	2.5 ^f (1046)	2.2-2.8
40+	6.1 ^f (7)	1.6-23.7	0.7 (2)	0.1-3.6	2.5 ^f (376)	2.1-3.0
	<i>P</i> < 0.01 ^g		NS ^h		<i>P</i> < 0.01	
Urinary tract infection (no.)						
Never	1.0 ^e (22)		1.0 ^e (22)		1.0 ^e (2068)	
1-2	2.0 (8)	0.8-4.9	1.3 (5)	0.4-3.9	1.4 ^f (424)	1.2-1.6
3+	5.5 ^f (12)	2.4-12.6	1.7 (4)	0.5-5.8	1.9 ^f (296)	1.6-2.3
	<i>P</i> < 0.01		NS		<i>P</i> < 0.01	
Diabetes mellitus	0.9 (4)	0.3-2.8	0.9 (3)	0.2-3.1	1.2 (293)	0.99-1.4
Coffee drinking ⁱ (cups/wk)						
0-7	1.0 ^e (9)		1.0 ^e (5)		1.0 ^e (625)	
8-21	0.9 (12)	0.3-2.2	2.1 (13)	0.7-6.9	1.0 (932)	0.9-1.1
22-49	1.4 (13)	0.5-3.5	2.8 (11)	0.8-9.5	1.1 (761)	0.9-1.2
50-63	2.1 (3)	0.4-10.8	2.7 (1)	0.1-48.7	1.4 ^f (110)	1.0-1.8
64+	1.1 (2)	0.1-6.6	5.2 (2)	0.5-58.1	1.5 ^f (153)	1.1-1.9
	NS		<i>P</i> < 0.05		<i>P</i> < 0.01	
Artificial sweeteners ^j (mg/wk)						
Nonuser	1.0 ^e (22)		1.0 ^e (16)		1.0 ^e (1552)	
1-239	0.2 (1)	0.1-1.4	0.6 (2)	0.1-2.7	0.9 (277)	0.7-1.0
240-719	1.9 (8)	0.7-4.5	1.0 (3)	0.2-3.7	1.0 (271)	0.8-1.2
720+	0.8 (2)	0.2-3.6	1.6 (3)	0.3-6.0	1.1 (177)	0.9-1.3
	NS		NS		NS	

^a Risk estimates adjusted for sex and age; risk estimates for coffee drinking further adjusted for cigarette smoking.

^b Numbers in parentheses, number of cases. Analysis by risk factor limited to responders who provided full information on risk factor and adjustment variables.

^c Risk estimates adjusted for sex, race and age; risk estimates for coffee drinking further adjusted for cigarette smoking.

^d Usual adult pattern of use.

^e Referent category.

^f *P* < 0.05.

^g Test for linear trend.

^h NS, not significant.

ⁱ Typical week in winter 1 year before interview.

^j Analysis restricted to nondiabetics, based on usual adult pattern of use.

Table 1 Average annual age-adjusted (1970 standard) incidence rates (per 100,000) for carcinomas of the urinary bladder in the United States, by sex, race, and three histological types, 1973-1982^a

	White		Black	
	Male	Female	Male	Female
Transitional cell carcinoma	26.9 (20,784)	6.7 (7,081)	11.9 (690)	4.1 (312)
Squamous cell carcinoma	0.5 (359)	0.3 (287)	0.9 (53)	0.5 (42)
Adenocarcinoma	0.3 (258)	0.1 (143)	0.5 (33)	0.3 (25)

^a From the SEER Program of the National Cancer Institute. Numbers in parentheses, number of cases.

squamous cell carcinoma and adenocarcinoma compared to blacks. For all cell types, incidence increased steadily with age, with a consistent excess for men.

Case-Control Study. Table 2 shows the RR values of bladder carcinoma by histological type associated with several suspected risk factors. The risk of squamous cell carcinoma was significantly elevated for those whose usual adult pattern of smoking was 20-39 cigarettes/day (RR = 3.6) and rose further among smokers of 40 or more cigarettes/day (RR = 6.1). No relation was seen between risk of adenocarcinoma and cigarette use. In comparison, the risk of transitional cell carcinoma rose to 2.5 among smokers of 20-39 and 40 or more cigarettes/day.

The risk of squamous cell carcinoma rose with the number of urinary tract infections, reaching 5.7 for those with 3 or more infections. Smaller increases in risk were seen for transitional cell carcinoma and adenocarcinoma. Diabetes mellitus

was not a risk factor for squamous cell carcinoma or adenocarcinoma, and the slight excess with transitional cell carcinoma was not significant. Risks associated with coffee drinking after adjusting for smoking showed a significant dose-response trend for adenocarcinoma, but the individual risks were based on small numbers and were not significant. No relationship was seen for squamous cell carcinoma, while a significant trend with increased coffee use was observed for transitional cell carcinoma. Artificial sweetener use was not significantly associated with risk of squamous cell carcinoma or adenocarcinoma or with transitional cell carcinoma.

Review of employment histories identified a significantly increased risk of squamous cell carcinoma among persons ever employed as a welder (RR = 5.9; 5 cases) or cook (RR = 4.5; 7 cases). In comparison, the risks of bladder cancer in the overall study population were not increased for welders or cooks.⁴ No significant occupational risks were seen for bladder adenocarcinoma.

DISCUSSION

This large scale population-based case-control survey of bladder cancer included 43 patients with squamous cell carcinoma and 32 with adenocarcinoma. Interpretation of results is limited by small numbers of patients available for study. However, our findings indicate that cigarette smoking is a potent risk factor

⁴ D. Silverman, personal communication.

for squamous cell carcinoma and seems unrelated to adenocarcinoma.

The risk of squamous cell carcinoma was also strongly associated with a history of recurrent urinary tract infection (11). This is consistent with the high frequency of squamous cell carcinoma of the bladder reported among persons prone to chronic cystitis, especially those with spinal cord injury (14) or with schistosomiasis haematobium (15). The risk of bladder adenocarcinoma was not significantly related to prior urinary tract infection.

A search of occupational histories suggested an increased risk of squamous cell carcinoma of the bladder among persons ever employed as welders or cooks, while no significant associations with occupation were observed for adenocarcinoma. These findings are based on a *a posteriori* inspection and small numbers and could be chance events. Previous studies of all bladder cancers combined have reported increased risks among both welders (2, 16) and cooks (3, 17), although these occupations are not associated with excess risk in our overall study population.

Coffee drinking has been examined in several epidemiological studies as a possible risk factor for bladder cancer (2, 4, 18, 19), but the results have not been consistent. We found no association between coffee drinking and squamous cell carcinoma. A significant trend toward increasing risk with coffee intake was observed for adenocarcinoma, but was based on small numbers. The trend associated with transitional cell carcinoma has been previously analyzed and appears to be a noncausal relationship (4). Use of artificial sweeteners was not consistently related to any cell type of bladder cancer.

In summary, this case-control study revealed some differences in the impact of risk factors on histological types of bladder carcinoma. Most striking were the effects of cigarette smoking and recurrent urinary tract infection on squamous cell carcinoma. However, the number of patients ascertained to have squamous cell carcinoma or adenocarcinoma may not have been sufficient to estimate risks with desired precision, and some results may be due to chance. Further epidemiological and laboratory studies aimed at pursuing these leads should help in defining causal factors and mechanisms for the less common types of bladder cancer.

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