

## FAMILIAL AND ENVIRONMENTAL INTERACTIONS IN BLADDER CANCER RISK

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**In a population-based study of 2,982 bladder cancer patients and 5,782 controls in 10 geographic areas of the United States which was designed to assess the role of environmental risk factors, information was also obtained on the history of urinary tract cancer in first-degree relatives. A family history of urinary tract cancer significantly elevated the risk of bladder cancer [relative risk (RR) = 1.45], with higher risks observed among patients under age 45. The risks of bladder cancer associated with positive family history were generally higher among persons with suspected environmental exposures, particularly heavy cigarette smoking (RR = 10.7 among those who smoked 3 or more packs per day). Further studies of bladder cancer should incorporate biochemical and genetic probes to assess mechanisms of familial susceptibility and interactions with environmental factors.**

Following the report in 1967 of bladder cancer in 4 members of a family (Fraumeni and Thomas, 1967), a number of familial aggregations of this tumor have been studied (Benton and Henderson, 1973; Leklem and Brown, 1976; Lynch *et al.*, 1979; Mahboubi *et al.*, 1981; Marchetto *et al.*, 1983; McCullough *et al.*, 1975; Petkova-Bocharova *et al.*, 1977; Purtilo *et al.*, 1979; Sharma *et al.*, 1976). While some of these clusters may be due to common environmental exposures (Benton and Henderson, 1973), others may be related to genetic mechanisms such as those affecting the metabolism of environmental agents.

Evidence for familial susceptibility in bladder cancer has come principally from case reports, and information from surveys is limited (Cartwright, 1979). In a large population-based case-control study of bladder cancer which was designed to evaluate the role of artificial sweeteners and other suspected factors in the risk of this tumor, we obtained data on urinary tract cancer in first-degree relatives. While detailed information on these family members was not available, the study provides an opportunity to assess the role of familial predisposition and its interaction with environmental determinants of bladder cancer.

### METHODS

Through the Surveillance, Epidemiology and End Results (SEER) Program and the New Jersey Cancer Registry, we identified residents of metropolitan Atlanta, Detroit, New Orleans, San Francisco, Seattle and the states of Connecticut, Iowa, New Mexico, Utah and New Jersey, aged 21-84 for whom a recent diagnosis of histologically proven carcinoma of the urinary bladder had been made during the one-year period beginning in December 1977. Details of the study and methods have been presented elsewhere (Hoover *et al.*, 1980; Hartge *et al.*, 1984). During the study period, 4,045 eligible cases were identified and contacted for interview within 90 days of diagnosis;

3,763 cases were alive at the time of contact and 2,982 agreed to be interviewed. Ninety-seven per cent of tumors were histologically transitional-cell carcinomas.

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 aged 21-64 were chosen from a census of individuals obtained through a random-digit dialling procedure, in which telephone numbers were randomly selected from all residential telephones in each area (98% of all cases also had telephones). Controls aged 65-84 were randomly selected from the enumeration of US citizens over age 65 obtained by the Health Care Financing Administration. Of the controls thus selected, 83% agreed to participate (5,782 controls).

Structured questionnaires were administered through personal interviews conducted in homes of respondents by trained interviewers. Respondents were asked whether anyone in their immediate family (*i.e.*, parents or siblings) had ever had cancer of the urinary tract; additional data were not available from medical records or family members. Information on family history was thus obtained for 2,900 cases (97%) and 5,684 controls (98%). Data from lifetime histories of tobacco use, artificial sweeteners, coffee drinking, occupation, and urinary tract infection were also evaluated in analyses presented here. Suspected high-risk occupations were defined *a priori* as follows: processing or dyeing occupations in the rubber, plastics, synthetics, textile and leather industries; and occupations in the chemical and allied industries with exposures to organic chemicals (Case and Hosker, 1954; Case *et al.*, 1954; Cole *et al.*, 1972; Howe *et al.*, 1980; Najem *et al.*, 1982; Wynder *et al.*, 1963).

We ascertained the occurrence of urinary tract cancer in immediate family members, upon which our risk estimates were based, and were unable to separate bladder from kidney tumors. Based upon population data, however, at least 75% of urinary tract cancers would be expected to occur in the lower urinary tract, primarily the bladder (Cutler *et al.*, 1975). Misclassification from inclusion of kidney cancer in our data may have resulted in underestimation of the true risk associated with a family history of bladder cancer. Thus, estimates presented here may be conservative.

The measure of association used is the maximum likelihood estimate of the relative risk (RR). Potentially confounding variables were controlled through multiple contingency table analyses with 95% confidence intervals (CI) for individual risk estimates calculated according to Gart (1970). Relative risk

estimates were adjusted for sex, race and age, unless otherwise specified.

### RESULTS

A positive family history of urinary tract cancer was reported by 162 bladder cancer cases (6%) and 218 controls (4%), and was associated with a significantly elevated risk of bladder cancer (RR=1.45; 95% CI 1.2-1.8). As shown in Table I, the familial risks showed a trend with age and were highest among persons under age 45 (RR=2.7), women (RR=1.8), non-whites (RR=2.0), Protestants (RR=1.7), and persons of French, German, or British heritage (RR=2.4, 1.8 and 1.7, respectively). Risks were also higher for the less common histologic types of bladder carcinoma (*i.e.*, squamous-cell carcinoma, adenocarcinoma) but were based on small numbers.

The RRs of bladder cancer associated with family history were also examined according to several environmental exposures previously suspected as risk factors.

#### Cigarette smoking

Table II shows RRs of bladder cancer associated with family history within each smoking category. Among persons grouped according to usual adult pattern of cigarette use, the risk of bladder cancer associated with family history was higher for those who smoked 40-59 cigarettes per day (RR=2.0; 95% CI 0.9-4.4), and rose further among those who smoked 60 or more cigarettes (*i.e.*, 3 packs or more) per day (RR=10.7, 95% CI 1.3-237).

Table III lists RRs of bladder cancer by family history of urinary tract cancer and cigarette usage, in comparison to persons with a negative family history who never smoked cigarettes. The risk of bladder cancer among moderate and heavy smokers was further elevated in the presence of a positive family history, particularly for the relatively small group of smokers who used 3 or more packs per day (RR=28.1; 95% CI 3.5-605).

#### Other exposures

The risks of bladder cancer associated with family history were higher among heavier users of artificial sweeteners (RR=2.1; 95% CI 1.0-4.4) and coffee (RR=1.9; 95% CI 1.0-3.6), compared to risks in non-users (Table II). Among persons ever employed in a high-risk occupation, the risk of bladder cancer associated with family history was not elevated (RR=1.0). However, among such persons ever employed in the rubber industry, 3 cases *versus* no controls reported a positive family history. Risk of bladder cancer associated with family history was higher among persons with a history of 3 or more urinary tract infections (RR=1.8), but the increase was not statistically significant.

### DISCUSSION

Results of this population-based study indicated an elevated risk of bladder cancer associated with a reported family history of urinary tract cancer. The overall increased risk of 45% is similar to that seen in a case-control study of bladder cancer in England (Cart-

TABLE I - RELATIVE RISK (RR) ESTIMATES OF BLADDER CANCER ASSOCIATED WITH FAMILY HISTORY OF URINARY TRACT CANCER<sup>1</sup>, BY SELECTED DEMOGRAPHIC AND TUMOR CHARACTERISTICS: 10 GEOGRAPHIC AREAS OF THE UNITED STATES, 1978

|                                 | Cases          | Controls | RR (95% confidence interval) |
|---------------------------------|----------------|----------|------------------------------|
| Total                           | 162            | 218      | 1.5 (1.2-1.8)                |
| Age                             |                |          |                              |
| Below age 45 (148) <sup>2</sup> | 8 <sup>3</sup> | 7        | 2.7 (0.8-8.9)                |
| Ages 45-64 (1,169)              | 69             | 78       | 1.7 (1.2-2.4)                |
| Ages 65 and older (1,583)       | 85             | 133      | 1.3 (1.0-1.7)                |
| Sex                             |                |          |                              |
| Males (2,179)                   | 118            | 164      | 1.4 (1.1-1.8)                |
| Females (721)                   | 44             | 54       | 1.8 (1.1-2.7)                |
| Race                            |                |          |                              |
| Whites (2,736)                  | 157            | 210      | 1.5 (1.2-1.8)                |
| Non-whites (164)                | 5              | 8        | 2.0 (0.5-7.1)                |
| Religion                        |                |          |                              |
| Protestant (1,449)              | 98             | 121      | 1.7 (1.3-2.3)                |
| Roman Catholic (1,090)          | 51             | 75       | 1.3 (0.9-1.9)                |
| Jewish (154)                    | 4              | 6        | 1.1 (0.2-4.2)                |
| Latter Day Saints (92)          | 7              | 12       | 1.4 (0.5-4.0)                |
| None or other (104)             | 2              | 4        | 1.2 (0.1-7.4)                |
| Ethnic origin                   |                |          |                              |
| England, Scotland, Wales (894)  | 61             | 76       | 1.7 (1.2-2.5)                |
| Germany (660)                   | 49             | 44       | 1.8 (1.2-2.9)                |
| Ireland (505)                   | 25             | 45       | 1.2 (0.7-2.0)                |
| Eastern Europe (450)            | 15             | 29       | 0.9 (0.5-1.8)                |
| Italy (334)                     | 13             | 20       | 1.2 (0.5-2.6)                |
| France (196)                    | 16             | 18       | 2.4 (1.1-5.2)                |
| Scandinavia (176)               | 11             | 20       | 1.2 (0.5-2.8)                |
| Histologic type                 |                |          |                              |
| Transitional-cell (2,827)       | 156            | —        | 1.5 (1.2-1.8)                |
| Squamous-cell (38)              | 3              | —        | 2.2 (0.5-7.5)                |
| Adenocarcinoma (34)             | 3              | —        | 2.4 (0.6-8.5)                |

<sup>1</sup>Maximum likelihood estimate adjusted for: race, sex, smoking (age); race, age, smoking (sex); sex, age, smoking (race, religion, histologic type). Controls with same characteristic used as comparison group; for histologic type, all controls used as comparison group. <sup>2</sup>Total number of cases for whom family history was obtained, in parentheses. <sup>3</sup>Number of respondents with this characteristic and a positive family history of urinary tract cancer.

**TABLE II - RELATIVE RISK (RR) ESTIMATES OF BLADDER CANCER ASSOCIATED WITH FAMILY HISTORY OF URINARY TRACT CANCER, BY SUSPECTED BLADDER CANCER RISK FACTORS; 10 GEOGRAPHIC AREAS OF THE UNITED STATES, 1978<sup>1</sup>**

|   | RR (95% confidence interval) |
|---|------------------------------|
| <b>Cigarette smoking<sup>2</sup></b>              |                              |
| Never smoked (38, 85) <sup>3</sup>                | 1.5 (1.0-2.0)                |
| <20 cigarettes/day (18, 38)                       | 1.0 (0.5-1.8)                |
| 20-39 cigarettes/day (69, 69)                     | 1.4 (1.0-2.1)                |
| 40-59 cigarettes/day (18, 13)                     | 2.0 (0.9-4.4)                |
| 60+ cigarettes/day (8, 1)                         | 10.7 (1.3-236.5)             |
| <b>Artificial sweeteners<sup>2</sup></b>          |                              |
| Non-user (84, 114)                                | 1.5 (1.1-2.1)                |
| 1-239 mg/week (22, 35)                            | 1.5 (0.8-2.7)                |
| 240-719 mg/week (24, 24)                          | 2.0 (1.1-3.6)                |
| 720+ mg/week (18, 15)                             | 2.1 (1.0-4.4)                |
| <b>Coffee drinking<sup>4</sup></b>                |                              |
| 0-7 cups/week (29, 49)                            | 1.4 (0.8-2.3)                |
| 8-21 cups/week (69, 95)                           | 1.5 (1.1-2.1)                |
| 22-35 cups/week (34, 41)                          | 1.5 (0.9-2.5)                |
| 36+ cups/week (23, 19)                            | 1.8 (0.9-3.7)                |
| <b>High-risk occupation<sup>5</sup> (13, 24)</b>  | 1.0 (0.5-2.2)                |
| Rubber processing (3, 0)                          |                              |
| Other high-risk occupations <sup>6</sup> (10, 24) | 0.8 (0.4-1.9)                |
| <b>Urinary tract infection</b>                    |                              |
| Never (96, 155)                                   | 1.4 (1.1-1.8)                |
| 1-2 infections (27, 30)                           | 1.4 (0.8-2.5)                |
| 3+ infections (26, 18)                            | 1.8 (0.9-3.4)                |

<sup>1</sup>Maximum likelihood estimate adjusted for sex, race and age. <sup>2</sup>Usual adult pattern of use. <sup>3</sup>Number of cases and controls with family history of urinary tract cancer in parentheses. <sup>4</sup>Typical week in winter one year before interview. Includes adjustment for smoking. <sup>5</sup>Ever employed in these occupations; see text for definition. <sup>6</sup>Remainder of persons ever employed in high-risk occupations.

wright, 1979). The risks do not seem as high as the 2- to 3-fold risks reported for other common types of carcinoma (Anderson, 1982). However, the higher familial risks generally found among younger patients with various cancers were also seen for bladder cancer in our study.

Risks of bladder cancer associated with familial occurrence were higher among persons with certain environmental exposures previously implicated for this tumor compared to risks in the unexposed. Risks were highest among heavy cigarette smokers, suggesting an interaction between smoking and familial predisposition to urinary tract cancer. Among heavy users of artificial sweeteners or coffee, a family history of urinary tract cancer was associated with 2-fold increases in bladder cancer risk but these were not significant. A smaller increase in risk was seen among persons who had recurrent urinary tract infections. Overall, no interaction was seen with high-risk occupations; risk was substantially increased among persons who held processing occupations in the rubber industry, but was based on only 3 cases.

Heritable variations in N-acetyltransferase activity have been theoretically linked to the development of some bladder tumors, since the level or concentration of acetyltable arylamine bladder carcinogens (such as  $\beta$ -naphthylamine, benzidine, phenacetin) would be higher in persons slow to inactivate them (Lower, 1982). Some studies of bladder cancer patients have suggested possible associations with the slow acetylator phenotype (Lower *et al.*, 1979; Evans *et al.*, 1983), including tumors related to occupational arylamine exposure (Cartwright *et al.*, 1982), although one study found no relationship with acetylator status (Miller and

**TABLE III - RELATIVE RISK (RR) ESTIMATES OF BLADDER CANCER ASSOCIATED WITH FAMILY HISTORY OF URINARY TRACT CANCER AND CIGARETTE SMOKING; 10 GEOGRAPHIC AREAS OF THE UNITED STATES, 1978**

| Pattern of cigarette use   | RR (95% confidence interval) <sup>1</sup> |                         |
|----------------------------|---|-------------------------|
|                            | Negative family history                   | Positive family history |
| <b>Non-smokers</b>         | 1.0 <sup>3</sup>                          | 1.5<br>(1.0-2.2)        |
| <b>Smokers<sup>2</sup></b> |   |                         |
| <20 cigarettes/day         | 1.8<br>(1.6-2.1)                          | 1.6<br>(0.9-3.0)        |
| 20-39 cigarettes/day       | 2.5<br>(2.2-2.8)                          | 3.5<br>(2.4-5.1)        |
| 40-59 cigarettes/day       | 2.5<br>(2.1-3.1)                          | 4.8<br>(2.2-10.5)       |
| 60+ cigarettes/day         | 2.1<br>(1.5-2.9)                          | 28.1<br>(3.5-604.9)     |

<sup>1</sup>Maximum likelihood estimate of relative risk adjusted for sex, race, and age. <sup>2</sup>Smoker refers to current or ex-smoker. Number of cigarettes per day refers to usual adult pattern of use. <sup>3</sup>Reference category.

Cosgriff, 1983). Abnormalities of tryptophan metabolism have long been suspected of playing a role in bladder cancer, and were observed in one high-risk family (Leklem and Brown, 1976), but not in others (Fraumeni and Thomas, 1967; McCullough *et al.*, 1975) or in a population-based survey (Friedlander and Morrison, 1981). Thus, it remains to be seen whether familial occurrences of bladder cancer are related to genetic mechanisms affecting susceptibility of bladder epithelium or the absorption, metabolism or elimination of carcinogens. Alternatively, common exposure to environmental carcinogens may be more relevant; the greater tendency of smokers to have relatives who also smoke (Tokuhata, 1963) may contribute to the higher risk of familial bladder cancer in heavy cigarette users.

In summary, this case-control study revealed a significant 45% increase in risk of bladder cancer among persons with a family history of urinary tract neoplasms, which was further enhanced by heavy cigarette smoking and possibly other environmental factors. Since this analysis was not a major objective of the original study, we had only limited data on affected family members, with no confirmation of tumor type available from medical records. While potential differences in recall between cases and controls could be related in part to the overall increased risk we observed, it is unlikely that such bias would explain the interactions found between family history and environmental factors such as cigarette smoking. Future epidemiologic studies of bladder cancer incorporating biological markers such as the acetylator genotype may be useful in characterizing mechanisms of familial susceptibility and interactions with environmental risk factors.

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