Genital and Urinary Tract Diseases and Bladder Cancer

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ABSTRACT

The relationship between selected urinary tract and genital diseases and the risk of bladder cancer was analyzed using data from a case-control study of 364 cases of bladder cancer and 447 controls hospitalized for acute, nonneoplastic, nongenital tract conditions, unrelated to known or suspected risk factors for bladder cancer. Cystitis was reported by 20% of the cases and 8% of the controls, corresponding to a multivariate relative risk (RR) of 3.8 (95% confidence interval, 2.4 to 5.9). No association was observed with urinary tract stones (RR = 1.2). With reference to genital diseases, the RR was elevated for gonorrhea (RR = 2.8, 95% confidence interval, 1.0 to 4.5) and condylomata acuminata (RR = 5.9, 95% confidence interval 1.0 to 3.6) but not for syphilis. The risk increased with the number of episodes of cystitis (RR = 5.0 for ≥4 episodes, χ² for trend = 33.04, P < 0.001), was higher during the last 15 years after the first episode (RR = 5.1 versus 2.3 for over 15 years), and was not heterogeneous across strata of age and sex. The interaction between urinary tract infections and tobacco appeared multiplicative, with RR = 2.4 for ever smoking, 3.2 for cystitis alone, and 10.3 for both exposures. The present study, besides providing further quantitative evidence of a relationship between urinary tract infections (and, possibly, some genital infections, too) and bladder cancer, indicates that the role of infections is probably in one of the latter (promoting) stages of the process of carcinogenesis and suggests a multiplicative interaction with smoking. In terms of prevention and public health, therefore, it is thus important to avoid at least one exposure for subjects with a history of urinary tract infections who smoke tobacco.

INTRODUCTION

Cigarette smoking and occupational exposure to aromatic amines and other chemicals are the best recognized risk factors for bladder cancer in developed countries (1). However, these factors alone cannot totally account for the geographical distribution of incidence and mortality from the disease, both on an international and national scale (2, 3). Within Italy, for instance, this is the single tobacco-related site showing only moderate differences between the North (where tobacco spread and the industrialization process occurred earlier) and the South of the country (4, 5).

Diet plays probably some role (1, 6), but further potential factors in bladder cancer epidemiology are infections and other diseases of the urinary tract, which may cause chronic irritation and hence favor the action of specific carcinogens. A clear relationship has been established in Egypt and other African regions between infection with Schistosoma haematobium and bladder cancer risk (7, 8), but the role of other infectious agents or specific cystitis on bladder carcinogenesis is more difficult to study epidemiologically, particularly because early symptoms of bladder cancer are similar to those of cystitis, and subjects with urinary tract conditions probably tend systematically to recall episodes of cystitis or other urinary tract conditions more accurately. Not surprisingly, therefore, published evidence is largely inconsistent, with relative risks ranging from 1 (9) to 5 (10) for infections and from 1 (9) to 3 (11) for urinary tract stones.

Thus, to provide further quantitative information on the issue, we have analyzed data on urinary tract and genital diseases from a large case-control study conducted in the Greater Milan area, Northern Italy.

SUBJECTS AND METHODS

The data were derived from a study of urinary tract neoplasms that has been ongoing since January 1985 in the Greater Milan area, Northern Italy, and the present report is based on data collected before June 1990.

The general scheme and method of this investigation has already been described (6, 12). Briefly, trained interviewers identified and questioned patients admitted to a network of hospitals under surveillance for urological cancers and a wide spectrum of other conditions. All interviews were conducted in the hospital. Less than 3% of eligible subjects (cases and controls) refused to be interviewed.

The patients included in the present analysis were 364 histologically confirmed cases of invasive transitional cell bladder cancer (303 males, 61 females; median age, 63 years; range, 28–74) after specific exclusion of papillomas, as well as of squamous cell cancers (which represented less than 2% of bladder cancer cases in this population). The controls were 447 patients (336 males, 111 females; median age, 62 years; range, 25–74), admitted to the same network of hospitals for a wide spectrum of acute, other than urological or genital tract diseases (29% traumas, 17% nontraumatic orthopedic conditions, 13% medical disorders, 7% surgical conditions, 34% other miscellaneous illnesses). The catchment area of cases and controls was comparable: 76% of cases and 78% of the controls came from the same region, Lombardy; 85% of the cases and 87% of the controls were from Northern Italy.

The structured questionnaire included information on sociodemographic factors, personal characteristics and habits (including smoking and coffee consumption), selected lists of indicator foods and relevant occupational exposures, and a problem-oriented medical history. Information was specifically elicited on age at first occurrence of five urogenital conditions (cystitis, urinary tract stones, gonorrhea, syphilis, and condylomata acuminata), and on the number of episodes of cystitis.

Statistical analysis was based on standard methods for case-control studies, including sex- and age-adjusted RR1 and estimates from multiple logistic regression models (13). Included in the regression equations were terms for age, sex, education, area of residence, smoking, and exposure to high risk occupations (dyestuff, chemicals, painting, pharmaceuticals, and coal/tar).

RESULTS

Cases were somewhat older than the comparison group, less educated (RR for <7 versus ≥7 years of education = 1.4; 95% CI 1.0 to 2.1), and more frequently smokers (RR = 3.3 for current and 3.9 for heavy smokers (Table 1).

The abbreviations used are: RR, relative risk; CI, confidence interval.

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3The abbreviations used are: RR, relative risk; CI, confidence interval.
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from multiple logistic regression equations including terms for age, sex, education,

cases and 2 controls only). None of these RR estimates was

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or bladder stones (RR = 1.2, 95% CI 0.6-2.6). With reference

of the controls corresponding to a multivariate relative risk of

in Table 2. Cystitis was reported by 20% of the cases and 8%
cystitis reported four or more episodes. With reference to time

episodes. About two-thirds (46 of 73) of cases with history of

episodes and rose to 3.2 for three and to 5.1 for four or more

The RR was approximately 2-fold elevated for one or two

episode.

of significance), but not for syphilis (reported by 3

(5.9-20.1) (0.9-4.6)

3.8 (95% CI 2.4-5.9)

5.8 (1.4-24.6) (1.1-30.6)

* M-H, Mantel-Haenszel estimates adjusted for age and sex; MLR estimates from multiple logistic regression equations including terms for age, sex, education, area of residence, smoking, and occupation (chemical industry, dyestuff, painting, pharmacueticals, and coal/tar).

History of selected urinary and genital diseases is considered in Table 2. Cystitis was reported by 20% of the cases and 8% of the controls corresponding to a multivariate relative risk of 3.8 (95% CI, 2.4-5.9). No association was observed with kidney or bladder stones (RR = 1.2, 95% CI 0.6-2.6). With reference to genital diseases, the relative risk was elevated for gonorrhea (RR = 2.1, 95% CI 1.0-4.5), and for condylomata acuminata (reported by 9 cases and 2 controls, for a point estimate of 5.9, of borderline significance), but not for syphilis (reported by 3 cases and 2 controls only). None of these RR estimates was materially modified by allowance for major identified co-

The relationship with cystitis was further examined in Table 3 in terms of number of episodes and time since first episode. The RR was approximately 2-fold elevated for one or two episodes and rose to 3.2 for three and to 5.1 for four or more episodes. About two-thirds (46 of 73) of cases with history of cystitis reported four or more episodes. With reference to time since first episode, the RR was over 5-fold elevated up to 15 years but declined to 2.3 at 15 years or more after the first episode.

Separate strata of sex and age group are considered in Table 4. The risk estimates were somewhat higher in males and in older age groups but not heterogeneous across various sex and age groups. Likewise, no significant heterogeneity across strata of sex and age was observed for gonorrhea or genital warts.

The interaction between history of cystitis and smoking is

presented in Table 5. Compared with individuals who reported not to have ever smoked or had cystitis, the RR was 2.4 for ever smoking and 3.2 for individuals with history of cystitis alone and rose to 10.3 for exposure to both risk factors. Thus, the interaction between these two risk factors seemed to be multiplicative (or overmultiplicative, but not additive) on the relative risk.

<table>
<thead>
<tr>
<th>No. of episodes of cystitis</th>
<th>Bladder cancer</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>285</td>
<td>407</td>
</tr>
<tr>
<td>1</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>≥4</td>
<td>47</td>
<td>17</td>
</tr>
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Unknown 6 5

<table>
<thead>
<tr>
<th>Relative risk estimates (95% CI)</th>
<th>M-Hb</th>
<th>MLR</th>
</tr>
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<table>
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<tr>
<th>No. (%) of subjects with the disease</th>
<th>Bladder cancer</th>
<th>Controls</th>
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<tr>
<th>Relative risk estimates (95% CI)</th>
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<table>
<thead>
<tr>
<th>Type of disease</th>
<th>No. (%) of subjects with the disease</th>
<th>Relative risk estimates (95% CI)</th>
<th>M-H*</th>
</tr>
</thead>
</table>

Cystitis 73 (20.1) 35 (7.8) 3.4 3.8

Urinary tract stones 17 (4.7) 20 (4.5) 1.0 1.2

Gonorrhea 21 (5.8) 12 (2.7) 2.0 2.1

Syphilis 3 (0.8) 2 (0.4) 2.9 1.1

Condylomata acuminata 9 (2.5) 2 (0.4) 5.8 5.9

<table>
<thead>
<tr>
<th>Type of disease</th>
<th>No. (%) of subjects with the disease</th>
<th>Relative risk estimates (95% CI)</th>
<th>M-H*</th>
</tr>
</thead>
</table>

Sex

Males 54 (17.8) 17 (5.1) 4.1 (2.3-7.1)

Females 19 (31.1) 18 (16.2) 2.4 (1.2-5.0)

Age group

<60 yr 28 (24.3) 19 (9.7) 3.2 (1.7-6.3)

≥60 yr 45 (18.1) 16 (6.3) 4.1 (2.2-7.7)

<table>
<thead>
<tr>
<th>Relative risk estimates (95% CI)</th>
<th>M-H*</th>
<th>MLR</th>
</tr>
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</table>

Table 5 Interaction between history of cystitis and cigarette smoking and the risk of bladder cancer: Milan, Italy, 1985-1990

Relative risk (95% CI) for history of cystitis

<table>
<thead>
<tr>
<th>No. of cases:number of controls</th>
<th>Never smokers</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Relative risk estimates (95% CI)</th>
<th>M-H*</th>
<th>MLR</th>
</tr>
</thead>
</table>

Never smokers 1* 3.2 (1.6-6.3) 59:162 22:20

Ever smokers 2.4 (1.6-3.6) 10.3 (5.3-20.1) 232:250 51:15

* Mantel-Haenszel estimates adjusted for age and sex.

b Reference category.

c Number of cases:number of controls.
DISCUSSION

The present study provides further quantitative evidence of a relationship between urinary tract infections (and, possibly, some genital infections as well) and bladder cancer. This is therefore consistent with most (10, 11, 14–16) [though not all (9)] previous investigations, in terms of both existence and size of the association, since a relative risk of 3–4 appears to be a reasonable estimate of the bladder cancer/urinary infection association from published studies [Refs. 10, 11, 14–16, and, for a summary tabulation, Ref. 9]. In terms of population attributable risk (17), urinary tract infections could account for about 10% of the cases of bladder cancer in this population. A further, more innovative indication that emerged is the association with gonorrhea and condylomatata acuminata, which may suggest similar etiopathogenic mechanism(s) for genital and lower urinary tract neoplasms.

A major problem of the present and most previous case-control investigations is recall bias, since cases of bladder cancer are probably more sensitized towards recalling urinary tract conditions that patients admitted to hospital for other diseases (and population-based controls as well). Thus, although the interviewers were specifically trained to avoid or reduce this potential problem, it is likely that the relative risks are somewhat overestimated, although to an extent difficult to quantify. However large this bias may be, it is still unlikely by itself to have produced relative risks of the order of those observed in this study, and such strong direct trends in risk.

Selection (diagnostic) bias is also possible, since patients with cystitis are probably cystoscoped more than patients without it. However, only cases of histologically confirmed invasive bladder cancer were included, and this should have reduced the scope for bias.

Other possible sources of bias are probably less important. Although this is a typical hospital-based case-control study and, as such, has all the widely discussed relative possible weakness (18), it also has the strengths deriving from almost complete participation, a comparable catchment area of cases and controls, as well as the absence of important confounding by a number of potentially relevant covariates (including socio-economic indicators, smoking and occupation) and the advantage of a similar recall of medical histories by cases and hospital controls (19).

The observation that the relative risk for cystitis tends to decrease with time since first episode indicates that urinary tract infections have a late-stage effect [in terms of the multistage theory of carcinogenesis (20, 21)] on bladder cancer risk, which is consistent with the promotional effect of wound healing and irritants in animal experiments of skin carcinogenesis (22, 23).

Within the multistage theory of carcinogenesis, it is also of interest to note that the interaction between tobacco and urinary tract infections was multiplicative, implying that these two factors act with different mechanisms and on different stages of the process (24). A similar analysis of the tobacco/occupation interaction based on a subset of the same study (25) indicated, in contrast, an additive effect between tobacco and occupation, suggesting that the same bladder carcinogens are probably shared by these two exposures.

A large, multicentric study from the United States (15), however, found that the interaction between cigarette smoking and urinary tract infections was additive (or slightly beyond additive) rather than multiplicative. Although the issue is still controversial, nonetheless, examination of the tobacco/urinary tract infection interaction and indicators from theories of carcinogenesis have important preventive and public health implications, since the grossly elevated relative risk found in this study among subjects with a history of cystitis and smoking indicates and underlines the importance for intervention on at least one factor in subjects exposed to both.

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