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Urinary Infection, Renal Lithiasis and Bladder Cancer in Spain

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A case-control study on bladder cancer was carried out in 12 hospitals located in 4 regions of Spain. The study included 497 cases and 530 population controls, matched by sex, age and residence. The present paper reports the results regarding the risk for bladder cancer in relation to history of infections and lithiasis of the urinary tract. Increased risk was found for infections starting 4 years or less before diagnosis (OR = 15.00; 95% CL: 6.07–51.66) but no statistically significant increase in risk was observed for infections starting 5 or more years before (OR = 1.44; 95% CL: 0.86–2.47). Our data suggest that the association of urinary infections with bladder cancer is probably not causal and is more likely to be a consequence of cancer, although a weak causal association cannot be excluded. A small but not statistically significant increase in risk was found to be associated with a history of renal lithiasis.
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INTRODUCTION

THE ASSOCIATION between a history of urinary infection and bladder cancer is controversial. Hospital based case-control studies [1–3] and population based studies [4] have shown an increased risk, but they did not take into account the period between onset of infection and appearance of the tumour. On the other hand, in a case-control study for which this information was available [5], the relative risk for infections of the bladder occurring during the 5-year period prior to diagnosis was 4.9 in males and 2.8 in females, but no increase in risk was reported for infections which started more than 5 years prior to diagnosis. Neither was any increased risk observed in a recent study on women which considered infections occurring at least 2 years prior to diagnosis [6].

There is, however, evidence to support the possibility of an association with urinary infection, particularly in cases of squamous cell carcinoma. An increase in these tumours has been described, associated with chronic urinary infections [7] and in areas of endemic schistosomiasis [8].

Two possible causal pathways of the infections have been suggested: one directly through bacterial flora which would favour the formation of nitrosamines from precursors such as nitrites and nitrates [9] and the other indirectly, in that the infection would increase absorption and/or exposure to carcinogens in the urine. An alternative explanation is that there may be no causal association, simply that the infection may be a consequence of the development of the tumour itself [5].

The other major disease of the urinary tract which has been considered as a potential risk factor for bladder cancer is urinary lithiasis [4, 5]. Increased risk has been reported for patients with a history of urinary bladder lithiasis but no history of urinary infection [5]. On the other hand, no increased risk in relation to renal lithiasis was observed.

In the present paper we present the results, with respect to histories of urinary infection and renal lithiasis, of a multicentre case-control study carried out in Spain. The study also investigated the risk associated with active and passive consumption of tobacco (G.L.-A. *et al.*), job exposure [10], diet (E.R. *et al.*) and consumption of coffee and artificial sweeteners.

MATERIALS AND METHODS

The study was carried out in 1985 and 1986 in the provinces of Barcelona, Madrid, Cadiz, Guipuzcoa and Biscay. Recruitment of cases was based on the registers of 12 hospitals belonging to or associated with the Social Security System, which cover

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Table 1. Cases and population controls by sociodemographic characteristics

	Cases	Controls
Sex		
Males	438 (88.1%)	465 (87.7%)
Females	59 (11.9%)	65 (12.3%)
Age (years)		
15–29	5 (1.0%)	3 (0.6%)
30–49	42 (8.5%)	42 (7.9%)
50–69	278 (55.9%)	295 (55.6%)
≥ 70	172 (34.6%)	190 (35.9%)
Mean	64.1	64.1
School years*		
Illiterate	36 (7.2%)	46 (8.7%)
Elementary	372 (74.8%)	378 (71.3%)
Secondary	39 (7.8%)	39 (7.4%)
High school	10 (2.0%)	20 (3.8%)
NE	40 (8.0%)	47 (8.9%)
Socioeconomic status†		
Managers, professionals	67 (13.5%)	69 (13.0%)
White collar	115 (23.1%)	137 (25.8%)
Blue collar	256 (51.5%)	256 (48.3%)
Farmers	19 (3.8%)	25 (4.7%)
Other and NEC	34 (6.8%)	37 (7.0%)
NOS	6 (1.2%)	6 (1.1%)

*χ^2 (4 df) 3.05, $P = 0.3841$; †χ^2 (4 df) 1.47, $P = 0.9168$.

more than 90% of the population in Spain. The participating hospitals represented a small fraction of total hospital beds in the provinces of Madrid and Barcelona, but accounted for the great majority of hospital facilities in the provinces of Cadiz, Guipuzcoa and Biscay.

The study includes all patients up to the age of 79 in whom bladder cancer was diagnosed and confirmed histologically and who resided in the same province as the hospital. Of the 691 cases diagnosed and identified, 497 were interviewed (438 men and 49 women, with an average age of 64). 254 were newly diagnosed incident cases, while 142 had been diagnosed in 1984 and 101 in 1983. Distribution of cases by histological type was as follows: 92% transitional, 1.4% squamous, 3.2% mixed and 0.6% adenocarcinoma, 0.8% carcinoma *in situ* and 2% not classified. Of the 194 cases that could not be interviewed, 103 had died, 39 could not be traced, 32 refused to cooperate, and 20 could not be included for other reasons.

There were two controls for every case, matched by sex, age (within 5 years) and place of residence. 583 hospital controls were patients selected from the hospital admissions register of various wards. Since hospital controls admitted to hospital for urinary lithiasis, cystitis and haematuria were excluded from the control series and since there were controls with other diagnoses that could have been related to urinary infection, hospital controls have been excluded from the present analysis. The population controls were chosen at random from the national census and from the same local section of the census as the cases. Of the 807 population controls selected, 530 were interviewed. Of those not interviewed, 140 could not be located, 60 refused to answer, 55 had died and 20 were lost for other reasons.

Distribution of cases and controls by sex, age, education and socioeconomic status is shown in Table 1 and does not indicate any meaningful difference between the two groups.

The information was gathered by means of questionnaires, and all interviews took place at the subject's home by a trained interviewer. The cases and controls in each set were interviewed by the same interviewer.

For urinary infections, subjects were asked whether such an infection had ever been diagnosed by a doctor and/or treated, giving details of the age at which this occurred for the first time. In the case of kidney gallstones, subjects were questioned about prior medical diagnosis and their age at the first diagnosis.

A random sample of 10% of all the interviews was re-evaluated in order to verify mistakes or errors of information (such as omissions and transcription and/or coding errors). Some 1.4% of the questionnaires were found to contain errors or mistaken information with regard to clinical history (urinary infections and renal lithiasis). We found no differences between cases and controls in this low frequency of errors.

Statistical analysis was carried out using a standard epidemiological package (Epicenter Software EPILOG). Matched analysis was used to measure the association between bladder cancer and each isolated variable, calculating the maximum likelihood estimate of relative risk (MLE) by the Newton–Rapson procedure of Miettinen [11]. Miettinen's formula was used for the exact calculation of the confidence limit (at the 95% 2-sided level). For simultaneous analysis of the different variables and control of the potentially confounding effect of a history of diabetes or tobacco consumption, the conditional logistic regression method was used. For the analysis of temporary variables, related to the date of diagnosis, the date for each case was used for the corresponding matched control.

Complete information on history of urinary infection was available for 396 pairs of cases and population controls. Incomplete pairs were excluded from the analysis (cases without a control or controls without a case) as well as pairs where information was missing for one of the members of the set (23 cases and 11 population controls). Subjects who had had a urinary infection for the first time during the year of diagnosis or later were considered as non-exposed.

RESULTS

History of urinary infection was different for cases than for controls. The number of discordant pairs where the case was exposed was higher than the number of such pairs where the control was exposed (Table 2). The frequency of discordant pairs where the case was exposed was higher in both males and females.

However, analysis of urinary infections according to latency since they first started indicated that the majority of infections commenced near the time of diagnosis for cases. The number of discordant pairs where the case was exposed within the group with onset of infection 4 years or less prior to diagnosis was almost twice that of the group which reported having started urinary infections 5 or more years previously.

The matched relative risk of bladder cancer was considerably higher for infection occurring 4 years or less prior to diagnosis (RR = 15.00, 95% CL: 6.07–51.66) than for infections starting 5 or more years before (RR = 1.44, 95% CL: 0.78–2.31). History of infections starting 5 or more years before the diagnosis was associated with a relative risk of 1.41 (95% CL: 0.82–2.52) in males and 1.67 (95% CL: 0.40–9.21) in females. Neither is statistically significant.

Tobacco consumption was found to be a very important risk factor (OR = 3.79 for cigarette smokers as compared to non-smokers) in our study (G.L.-A. *et al.*). However, adjusting for

Table 2. Urinary infection. Matched pairs distribution and odds ratio according to year of onset of infection and sex

Year of onset	Matched pairs status* +/+	+/−	−/+	−/−	Total sets	OR	95% CL
4 years or less							
Males	6	64	4	215	289	16.00	5.83–65.43
Females	1	11	1	17	30	11.00	1.42–189.90
Total	7	75	5	232	319	15.00	6.07–51.66
5 years or more							
Males	1	31	22	215	269	1.41 (1.33)	0.82–2.52 (0.74–2.38)
Females	2	5	3	17	27	1.67 (1.35)	0.40–9.21 (0.35–6.44)
Total	3	36	25	232	296	1.44 (1.34)	0.86–2.47 (0.78–2.31)

Reference category: no history of urinary infection or onset during the year of diagnosis or later.
The number in parentheses = adjusted for tobacco.
*Urinary infection in: both case and control (+/+), neither case nor control (−/−), only case (+/−), only control (−/+).

tobacco smoking changed only slightly the risk for urinary infection: from 1.44 to 1.34.

We noted that, although the proportion of urinary infections was higher both in cases and controls who reported a history of diabetes, the risk associated with the infection did not change after adjustment for history of diabetes (results not shown).

A history of renal lithiasis at least a year prior to diagnosis was reported by 12.7% of the cases and 10.5% of the population controls. The matched relative risk associated with a history of lithiasis was 1.23 (95% CL: 0.86–1.74). There was no increased relative risk with respect to different latency periods.

DISCUSSION

The results of this study confirm previous findings of an association between bladder cancer and history of urinary infection. However, if the date of onset of the infection is taken into account, and only infections starting 5 years or more prior to diagnosis are considered, the association becomes very weak and not statistically significant.

The limit between recent and past infection, which was set at 5 years, was not based on objective information. On the basis of the available data we simply tried to take into account a latency period which on the one hand may have been compatible with a cause–effect sequence and on the other hand could reasonably have excluded the cases of urinary infection which may have been due to preclinical and undiagnosed bladder cancer. The concentration of the onset of urinary infections during the period close to diagnosis or treatment, which was observed in cases, suggests that this association could be a non-causal association or, at least, that it could be overestimated if the time when it occurred is not taken into account.

In relation to urinary infection, an association with squamous cell tumours has been suggested. Of the 470 cases who provided information concerning histories of infection, 7 were squamous carcinomas and, of these, 6 did not report any history of urinary infection.

The results of our study, as well as previous investigations, suggest that the evidence regarding the link between urinary infection and bladder cancer should be interpreted with caution. Only histories of urinary infections mentioned by the persons interviewed were taken into consideration and, in spite of the fact that only infections which were reportedly diagnosed and/or treated by a medical doctor were included, they could have been conditioned by memory through confusion with other diseases and/or the signs and symptoms caused by the illness and/or its treatment. Account has also been taken of the fact that in our hospitals the patients are not usually told the true diagnosis (i.e. that they are suffering from cancer), but are informed that they are suffering from some other illness related to the bladder. This could generate some overestimation in relation to the clinical histories referred to by the cases.

An additional problem which might affect the result in the same direction is the bias due to differential recall of previous illness between cases and controls. In spite of that, we observed no association with a history of renal lithiasis.

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