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An Epidemiological Case-control Study of Bladder Cancer in Males from a Predominantly Rural District*

SØREN MOMMSEN,† JØRGEN AAGAARD§ and ARNE SELL†

Department of Oncology and Radiotherapy, Aarhus Municipal Hospital, University of Aarhus, DK 8000 Aarhus C, Denmark and §Institute of Social Medicine, University of Aarhus, DK 8000 Aarhus C, Denmark

Abstract—*A case-control study was performed on 165 male bladder cancer patients and an equal number of male control persons matched in age and geographic area. Thirty determinants of assumed importance were examined. A multivariate logistic analysis was performed. A significant increment in the relative risk (RR) for bladder cancer was associated with cigarette smoking (RR = 1.89), a history of prostatic surgery (RR = 2.38), nocturia (RR = 2.05), previous venereal disease (RR = 2.42), industrial work (RR = 1.82), work with oil or gasoline (RR = 2.71) and work with various unspecified chemical materials (RR = 1.58).*

INTRODUCTION

EPIDEMIOLOGICAL investigations revealing the association between cigarette smoking and bladder cancer are well-documented [1–3]. Furthermore, it is noticed that various chemical materials like 2-naphthylamine, benzidine and others can be of etiologic importance [4], and various occupational exposures in the development of bladder cancer are under suspicion [5]. It has been mentioned that urinary stasis might be a possible disposing factor of the disease [6–8].

The purpose of this study is to identify by a case-control design the most prominent determinants of increased relative risk (RR) to developing bladder cancer.

Thirty determinants of assumed importance were selected. Furthermore, based on clinical experience that bladder cancer patients had a history of a prostatic surgery more frequently than expected, variables concerning urinary stasis were obtained.

MATERIALS AND METHODS

The material comprised 165 consecutive cases of men with newly diagnosed bladder cancer (91.5% with invasive bladder cancer, 94.5% with transitional cell carcinoma), admitted to the department of oncology and radiotherapy during a 2-yr period, starting September 1977. The average age was 66.1 yr (range 42–85 yr). The department receives patients from a well-defined geographic area of 23,000 km^2 with about 1.5 million inhabitants. Sixty-two percent of the inhabitants (aged more than 50 yr) in this area live in rural districts [9]. Except from terminal, intractable cases, all newly diagnosed cases of bladder cancer occurring in the area are referred to the department. Patients with non-invasive tumours go elsewhere. So the number of patients studied reflects the 2-yr incidence of invasive bladder cancer among men in the area. The residence of the patients by degree of urbanization appears in Table 1. The control persons had an identical distribution.

Information from patients was obtained at

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‡Reprint requests should be addressed to: Søren Mommsen, The Institute of Cancer Research, University Hospital of Aarhus, Nørrebrogade 44, DK 8000 Aarhus C, Denmark.

Table 1. Distribution of residence for 165 male patients with bladder cancer and their corresponding 165 selected control persons

Residence	%
Rural district:	
Farm	18.2
Village (< 1000 inhabitants)	18.8
Smaller town (1–10,000 inhabitants)	22.4
Larger town (10,000–100,000 inhabitants)	31.5
City (> 100,000 inhabitants)	9.1
Total	100

the hospital through a questionnaire followed by an interview carried out by the same physician (SM). Data obtained, and listed in Table 2, concerned smoking habits (quantity per day, number of years), prostatic surgery, symptoms of cystitis, nocturia, defined as nocturnal urination twice or more at least two years before the presenting symptoms of the bladder cancer, occupation with exposure for chemical materials and some socio-economic variables.

The patients were matched to control persons through the regional parts of the national register on a one-to-one basis, not only in respect to sex and age but also to geographic area, including degree of urbanization. The controls received an identical questionnaire and a few days later they were interviewed by telephone. If they did not have a telephone, which was the case among 5%, a supplementary questionnaire was mailed. If no reply was received another questionnaire was mailed after a month, and in case of non-response it was again repeated. If still no response was obtained the same procedure was performed with another matched control.

Table 2. Groups of questions used in the male bladder cancer aetiology study

Age
Sex
Socioeconomic status
Type of work
Occupational history
Work with chemical materials
Residence
Alcohol drinking habits
Smoking habits
Coffee consumption
Use of artificial sweeteners as a sugar substitute
Drug treatment
Family history of cancer disease
Radiotherapy treatment
Diseases of the skin
Allergy
Previous and present diseases of the urinary tract
Previous and present diseases of the lungs
Chronic diseases

The material was processed at the regional computer center. The computer program for the multivariate logistic analysis was written by Ipsen [10]. The principle of this analysis is through a step-by-step omission of independent variables, which are non-informative in a given model, to achieve the most informative description of the empirical data through a minimum of variables. The estimated relative risk E(RR) for bladder cancer is expressed in the reduced logistic model as the product of the independent relative risk of the most pronounced determinants if present. The goodness-of-fit of the model is expressed by the likelihood ratio G^2. When one variable is omitted the loss of information is estimated through the increase in G^2, ΔG^2, as a χ^2 with one degree of freedom. The applied statistical procedure is discussed elsewhere [11].

RESULTS

The selection and the response percentages for the controls appear in Table 3. Eighty-eight percent of the first-selected controls responded to the questionnaire and 65% responded primarily.

In Table 4 the bivariate associations of the 13 most pronounced determinants for bladder cancer are shown. The relative risk (RR) was estimated through the cross-product ratio. The confidence limits were test based from the differences between the basic value and the values of the independent variables [12].

Twenty-four (14.5%) of the patients and 11 (6.7%) of the controls had a history of prostatic surgery. The interval between the operation and the diagnosis of bladder cancer averaged 2.2 yr (range 0–14 yr). In 8 patients the diagnosis of bladder cancer was made simultaneously with the prostatic surgery. All the operated patients had benign prostatic hypertrophy.

In Table 5 the multivariate logistic regression analysis of the 13 most discriminating variables which were dichotomized (yes/no) are seen. The relative risks in the total model were ordered in rank after decreasing ratio log coefficient/standard error. The analysis was performed through a step-by-step omission of the weakest independent variables. Thus the strongest independent variable in this model was nocturia. The relative risk of developing

Table 3. Selection and reply for 165 male control persons matched to 165 male patients with bladder cancer

Selected control persons	Primary answer No.	%	Secondary answer No.	%	Tertiary answer No.	%	All answers No.	%
First-selected	107	65	27	16	10	7	144	88
First substitute	14	7	7	2	1	1	18	10
Second substitute	3	2					3	2
All controls	124	74	30	18	11	8	165	100

Table 4. The bivariate association expressed on the relative risk (RR) of the 13 most pronounced determinants for bladder cancer among 165 male patients and their 165 selected control persons

Independent variable	Cases No.	Controls No.	ΔG^{2*} (d.f. = 1)	RR	95% confidence limits
Nocturia	60	36	8.54	2.05	1.27–3.32
Cigarette smoker	112	87	7.96	1.89	1.21–2.94
Prostatic surgery	24	11	5.54	2.38	1.16–4.90
Cheroot smoker	93	79	2.39	1.41	0.91–2.18
Lowest socio-economic level	46	33	2.84	1.55	0.93–2.58
Work with oil or gasoline	20	8	5.79	2.71	1.21–6.10
Previous venereal disease	16	7	3.89	2.42	1.01–5.82
Chewing tobacco user	39	26	3.27	1.65	0.96–2.84
Industrial worker	39	24	4.47	1.82	1.04–3.17
Work with petroleum or asphalt	9	3	3.26	3.12	0.91–10.75
Alcohol user	159	151	3.51	2.46	0.95–6.31
Symptoms of cystitis	9	4	2.06	2.32	0.74–7.32
Work with chemical materials	65	48	3.91	1.58	1.00–2.49

Basis: $G^2 = 457.47$, d.f. = 329, RR = 1.00.
*$\Delta G^2 = G^2_{\text{basis}} - G^2_{\text{independent variable}}$.

bladder cancer for men with nocturia was 2.05 times greater than for men without nocturia. This increment in relative risk was highly significantly different from the basis value ($\Delta G^2 = 457.47 - 448.93 = 8.54$, d.f. $= 329 - 328 = 1$, $P < 0.005$). The relative risk was increased to 4.38 (2.18×2.01) if they had nocturia and also smoked cigarettes compared with men who never smoked and never had nocturia. The increment in risk from 2.05 to 4.38 was highly significant ($\Delta G^2 = 448.93 - 439.79 = 9.14$, d.f. $= 328 - 327 = 1$, $P < 0.005$). Thus the risk was more than doubled if a man with nocturia smoked cigarettes.

Table 6 shows the results for the 7 independent variables that were significantly different from the basis. The remaining independent variables from Table 5 have not been transferred to the analysis performed in Table 6 because these parameters were each not significantly different from the basis. The G^2-values and the relative risks were calculated from the 165 patients and 165 control persons. Furthermore, some combinations of clinically important determinants are shown.

DISCUSSION

In this study, for the first time in a case-control epidemiological investigation from a predominantly rural district, we have shown an increased relative risk of developing bladder cancer for patients with possible prostatic hypertrophy. In contrast to earlier published studies, this sample was predominantly derived from rural districts without any larger industries.

A reply rate of 88% for the first-selected controls gives the general population in this study a major strength as the control group [13]. However, some shortcomings or biases in the study must be taken into account [14]. Owing to practical and economical limitations, the information was not obtained in exactly the same fashion from the cases and from the controls. Possibly, the different responses from cases and controls, for example, concerning venereal

Table 5. Logistic regression analysis: the relative risk (RR) for men calculated from the 13 most pronounced determinants by 165 male bladder cancer patients and their 165 selected control persons

Independent variable	RR	RR	RR	RR	RR	RR	RR	RR	RR	RR	RR	RR	RR	RR
Basis*														1.00
1 Nocturia	1.81	1.80	1.84	1.82	1.85	1.83	1.84	1.80	1.85	1.87	1.94	2.18	2.05	
2 Cigarette smoker	2.14	2.15	2.17	2.31	2.33	2.36	2.30	2.38	2.44	2.42	2.18	2.01	—	
3 Prostatic surgery	2.21	2.21	2.32	2.40	2.40	2.47	2.48	2.45	2.50	2.34	2.40	—		
4 Cheroot smoker	1.59	1.59	1.61	1.64	1.64	1.67	1.65	1.62	1.65	1.56	—			
5 Lowest socio-economic level (unskilled workers)	1.64	1.64	1.64	1.61	1.66	1.66	1.81	1.78	1.74	—				
6 Work with oil or gasoline	1.81	1.86	1.83	1.79	1.91	2.27	2.26	2.32	—					
7 Previous venereal disease	2.23	2.24	2.21	2.26	2.28	2.31	2.32	—						
8 Chewing tobacco user	1.59	1.58	1.59	1.63	1.64	1.64	—							
9 Industrial worker	1.37	1.39	1.40	1.40	1.39	—								
10 Work with petroleum or asphalt	1.90	1.95	1.92	1.87	—									
11 Alcohol user	1.65	1.66	1.62	—										
12 Symptoms of cystitis	1.69	1.69	—											
13 Work with chemical materials	1.05	—												
Excluding independent variable	None	13	12	11	10	9	8	7	6	5	4	3	2	
G^2-values	414.54	414.57	415.23	416.08	416.89	417.93	420.58	423.63	427.27	431.43	434.90	439.79	448.93	457.46
Degrees of freedom (d.f.)	316	317	318	319	320	321	322	323	324	325	326	327	328	329
ΔG^2† (d.f. = 1)	0.03	0.66	0.85	0.81	1.04	2.65	3.05	3.64	4.16	3.47	4.89	9.14	8.54	
P-values	NS	NS	NS	NS	NS	NS	NS	NS	< 0.05	NS	< 0.05	< 0.005	< 0.005	

*Basis: probability of bladder cancer/probability of non-bladder cancer.
†ΔG^2 = differences between G^2-values.
Dependent variable: risk of bladder cancer in men.

Table 6. The relative risk (RR) for men calculated from the 7 most pronounced determinants and some combinations by 165 male bladder cancer patients and their 165 control persons

Independent variable	ΔG^2*	Δd.f.†	RR	95% confidence limits
a (Nocturia)	8.54	1	2.05	1.27- 3.32
b (Cigarette smoker)	7.96	1	1.89	1.21- 2.94
c (Prostatic surgery)	5.54	1	2.38	1.16- 4.90
d (Industrial worker)	4.47	1	1.82	1.04- 3.17
e (Previous venereal disease)	3.89	1	2.42	1.01- 5.82
f (Different chemical materials)	3.91	1	1.58	1.00- 2.49
g (Work with oil or gasoline)	5.79	1	2.71	1.21- 6.10
a, b	17.67	2	4.38	1.85-10.35
a, c	11.56	2	3.64	1.44- 9.23
a, d	12.74	2	3.68	1.51- 8.99
b, c	15.91	2	6.17	2.02-18.85
b, d	11.95	2	3.32	1.42- 7.77
c, d	9.07	2	3.85	1.29-11.52
a, b, c	22.56	3	10.20	2.60-40.02
a, b, d	21.46	3	7.62	2.24-25.96
b, c, d	18.90	3	9.56	2.24-40.83
a, c, d	15.18	3	5.99	1.66-21.64
a, b, c, d	25.66	4	16.25	2.98-88.53

*$\Delta G^2 = G^2_{\text{basis}} - G^2_{\text{independent variable}}$

†Δd.f. = The differences between the numbers of degrees of freedom.

Basis: $G^2 = 457.47$, d.f. = 329, RR = 1.00.

Dependent variable: risk of bladder cancer in men.

disease, could be due to bias for this reason. Furthermore an 'unmasking bias' could be the excess of cases with a history of prostatic surgery comprising patients who had their bladder cancer diagnosed simultaneously with their prostatic surgery.

The increased risk of cigarette smoking to developing bladder cancer is well-established [1–3], and further confirmed in this investigation.

Many different industrial occupations are associated with an increased risk for bladder cancer [15]. The significantly increased relative risk for industrial workers and for men working with oil or gasoline and different unspecified chemical materials discovered in this study will undergo further analysis.

The investigation indicates a positive association between bladder cancer and prostatic surgery, nocturia and previous venereal disease. Some authors have mentioned a possible connection between urinary stasis and bladder cancer [8, 16, 17], but the problem is only very sparsely investigated in human or animal trials. Fellows [18] reported a significantly higher incidence of infravesical obstruction in 199 male patients with carcinoma of the bladder than in the age-matched control group. The obstruction was defined as trabeculation of the bladder, a thick bladder wall and a large volume of residual urine. The urological problems will be discussed in detail elsewhere [19].

The well-known sex ratio of 3–4:1 (♂/♀) in bladder cancer patients [2] might be explained by a long-standing predominance of men in industry and among cigarette smokers. Furthermore, the prostatic hypertrophy causing urinary stasis might also yield an explanation to the sex ratio.

The theory of a vesical or infravesical obstruction as a contributing factor in developing bladder cancer is comprehended as a consequence of the prolongation of the transit time of the urine in the bladder followed by an increased influence on the bladder mucosa of possible carcinogens.

Prostatic hypertrophy, here defined as prostatic surgery or nocturia, is considered as a disposing factor, but the relative risk is increased considerably by other factors such as cigarette smoking. Thus it is possible that not only extrinsic factors but also intrinsic factors can be contributing causes to the disease and perhaps be promoted by prostatic hypertrophy.

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