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Prostatic Hypertrophy and Venereal Disease as Possible Risk Factors in the Development of Bladder Cancer

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Summary. In three urological predictors, nocturia, prostatic surgery for prostatic hypertrophy and a previous venereal disease, a significantly increased relative risk (RR) of developing bladder cancer was detected. An epidemiological case-control investigation was performed on 165 male bladder cancer patients and an equal number of male controls matched concerning age and geographical area. The sample was obtained from a predominantly rural district. The theoretical individual risk factors were calculated by the aid of a multivariate logistic analysis. Twenty-four patients versus 11 controls had a history of prostatic surgery (RR = 2.38) for benign prostatic hypertrophy, 60 patients versus 36 controls complained of nocturia at least 2 years before presenting symptoms of bladder cancer (RR = 2.05), and 16 patients versus seven controls had a history of venereal disease (RR = 2.42). The results seems to indicate that prostatic hypertrophy and previous venereal disease may at least in part be factors of importance associated with bladder cancer.

Key words: Case control investigation, Bladder cancer, Prostatic hypertrophy, Venereal disease.

Introduction

It has been reported previously that a significantly increased relative risk (RR) of getting bladder cancer was associated with cigarette smoking, prostatic surgery, nocturia, previous venereal disease, industrial work, work with oil or gasoline, and work with various unspecified chemical materials [8].

In this paper the importance of factors related to the lower urinary tract (prostatic surgery, nocturia, and previous venereal disease) and the occurrence of bladder cancer are investigated in detail. These variables implicating a possible obstruction were chosen because bladder cancer patients more frequently than expected appeared to present a previous history of possible urinary obstruction from benign prostatic hypertrophy.

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Material and Methods

The material comprised 165 consecutive male patients 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-year period starting September 1977. The average age was 66.1 years (42–85). The department receives patients from a district of about 1.5 million inhabitants.

All patients underwent cystoscopy with biopsy of the tumour and bimanual rectal palpation in general anaesthesia. After the histological specimens were reviewed a questionnaire followed by an interview was carried out. The questionnaire was designed to ascertain information concerning all accepted aspects of bladder cancer aetiology as well as to introduce a search for new features. Among others [8], the following parameters were registered: a history of prostatic surgery, nocturia defined as nocturnal urination twice or more (at least 2 years before the presenting symptoms of bladder cancer), and previous venereal disease. In this paper prostatic hypertrophy is defined by aid of the two first-named predictors.

The patients were matched to controls through the regional division of the national register on a one-to-one basis, not only with respect to sex and age, but also to the same geographical area. The controls received an identical questionnaire, and a few days later they were interviewed by telephone. The procedure is described in detail elsewhere [8].

The material was processed at the regional computer centre. The computer programme for a linear logistic multivariate regression analysis was devised by *Johannes Ipsen* [14]. By this analysis it is possible to calculate the independent risk at given levels of the chosen parameters. This technique enables relative risk estimates to be made simultaneously for a number of factors while eliminating possible confounding effects between factors [8]. The applied statistical procedure is discussed elsewhere [1].

Results

Eighty-eight per cent of the first selected controls responded to the questionnaire, and 65% responded at the first contact [8].

Table 1. Summary of surgery on the prostate in 24 patients with bladder cancer

Name of the patient	Operation of the prostate[a]	Duration between prostatic surgery and diagnosis of bladder cancer	Weight of prostatic tissue	T- or p- category of bladder cancer
1 NKN	TV	0	Not stated	pT3
2 PN	TV	0	20 g	pT1
3 EER	TURP	0	15 ml	T1
4 UK	TURP	0	Not stated	Ta
5 FLR	TURP	0	Not stated	T1
6 SBJ	TV	0	70 g	pT2
7 ACP	TV	0	200 g	pT1
8 EFH	TV	0	75 g	pT4a
9 OGC	TV	1 month	41 g	pT4a
10 PB	TV	3 months	24 g	pT4a
11 EHN	TURP	5 months	3 ml	T4a
12 IC	TURP	6 months	50 ml	T3
13 HDJ	TV	8 months	17 g	T3
14 NLT	TV	1 year	Not stated	T2
15 CTB	TURP	1 year	Not stated	T4b
16 CCR	TV	1 year	20 g	T1
17 AH	TV	2 years	50 g	T1
18 FSN	TURP	2 years	Not stated	T3
19 AVK	TV	2 years	25 g	T1
20 SMJ	TV	4 years	15 g	T3
21 SHJ	TV + lithotripsy	7 years	5 g	T4b
22 PHS	TV	9 years	12 ml	T1
23 FPN	TV	12 years	Not stated	Ta
24 JHM	TURP	14 years	Not stated	T3

[a] TURP = Transurethral resection of the prostate; TV = Transvesical prostatectomy

Table 2. The relative risk (RR) calculated after three urological determinants and some combinations by 165 male bladder cancer patients and their 165 control persons. Dependent variable: Risk for bladder cancer by men

Independent variable	ΔG^{2a}	Δdf^{b}	RR	95% confidence limits
a (nocturia)	8.53	1	2.05	1.27– 3.32
b (previous venereal disease)	3.88	1	2.42	1.00– 5.83
c (prostatic surgery)	5.53	1	2.38	1.16– 4.90
a, b	13.03	2	5.53	1.73–17.64
a, c	11.56	2	3.64	1.44– 9.23
b, c	9.27	2	5.70	1.41–23.10
a, b, c	15.91	3	9.64	1.97–47.19
Basis: $G^2 = 457.46$; df = 329; RR = 1.00				

[a] $\Delta G^2 = G^2_{\text{basis}} - G^2_{\text{independent variable}}$ [b] Δdf = The differences between the numbers of degrees of freedom

Twenty-four (14.5%) of the patients and 11 (6.7%) of the controls (Table 1) had a history of prostatic surgery for histologically benign prostatic hypertrophy. The interval between the operation and the diagnosis of bladder cancer averaged 2.4 years (0–14 years). In eight patients the diagnosis of bladder cancer was made at the time of surgery on the prostate.

Sixty patients and 36 controls had nocturnal urination and 16 patients and seven controls had a history of venereal disease (in all cases gonorrhoea).

Table 2 shows the RR's of the three independent variables all statistically significantly different from the basis. The G^2-values and the RR's were calculated from the 165 patients and 165 controls. The 95% confidence limits were calculated from the differences between the basis values and the values of the independent variables. If the 95% confidence interval includes the value 1.0, the "null hypothesis" of no difference between the groups cannot be rejected and the risk is not statistically greater or smaller than 1.0. Furthermore, the combinations of determinants are shown.

Table 3 shows the results of the three determinants which were dichotomised (yes/no). The RR's were calculated from the 165 male bladder cancer patients and their 165 controls. The analysis was performed through a step-by-step omission of the weakest urological independent variables. Finally, we finished with the strongest variables. Thus, the

Table 3. Logistic regression analysis. The relative risk (RR) calculated from the three most pronounced urological determinants by 165 male bladder cancer patients and their 165 selected control persons. Dependent variable: Risk for bladder cancer by men

Independent variable	RR	RR	RR	RR
Basis[a]				1.00
1 Nocturia	1.93	2.11	2.05	
2 Previous venereal disease	2.59	2.62	–	
3 Prostatic surgery	1.93	–		
Excluding independent variable	None	3	2	
G^2-values[b]	441.55	444.43	448.93	457.46
Degrees of freedom (df)	326	327	328	329
ΔG^2 [c] (df = 1)	2.88	4.50	8.53	
p-values	NS	< 0.05	< 0.005	

[a] Basis = probability of bladder cancer/probability of non-bladder cancer, [b] $G^2 = \chi^2$ for great values, [c] ΔG^2 = differences between G^2-values

strongest independent variable in this model was nocturia. The risk of developing bladder cancer for men with nocturia was 2.05 times greater than for men without nocturia. This RR was highly significantly different from the basis (ΔG^2 = 457.46 – 448.93 = 8.53; df = 329 – 328 = 1; $p < 0.005$). The RR was increased to 5.53 (multiply 2.11 by 2.62) in cases of both nocturia and previous venereal disease when compared to men who had never had nocturia or venereal disease. The increment in risk from 2.05 to 5.53 was statistically significant (ΔG^2 = 448.93 – 444.43 = 4.50; 328 – 327 = 1; $p < 0.05$). Thus, the risk was more than doubled if a man with nocturia had a history of venereal disease. There was no significant increase in RR if all urological independent variables were present when compared to the presence of only nocturia and previous venereal disease.

Discussion

This case-control investigation indicates an increased relative risk of developing bladder cancer in patients with prostatic hypertrophy and previous venereal disease.

The sample in the present study deviates from previously published case-control studies in that it is geographically derived from a predominantly rural district [8]. A reply rate of 88% for the controls selected first gives the general population in this study a major strength as control group [3].

The diagnosis of bladder cancer in this material was made in other hospitals, and the patients were admitted for evaluation and definitive treatment on average 5 weeks later [9].

The information from the controls concerning prostatic surgery was not verified from the medical records. The 11 prostatic operated controls are, however, a maximum number and the RR of developing bladder cancer associated with prostatic surgery would only be increased if any of the information from the controls were wrong.

Eight patients had surgery of the prostate for benign hypertrophy at the same time as the bladder cancer was diagnosed (Table 1). Six of these patients had gross haematuria as the initiating symptom, and it is most likely that the haematuria was due to their bladder cancer. These patients, however, were destined to have their prostates removed, possibly on uncertain indications, but it does not exclude the possibility that the patients also had prostatic hypertrophy e.g. the patient with a 200 g prostate. These eight patients and the two patients with pT4a carcinomas (prostatectomy 1 and 3 months before diagnosis of bladder cancer) reduced the difference between controls and patients concerning obstruction due to prostatic hypertrophy as a pathogenetic factor in the development of bladder cancer.

As there is no accepted criteria for prostatic hypertrophy we defined the disease as a patient with a history of prostatic surgery and/or nocturia at least 2 years before the presenting symptoms of bladder cancer and a histologically benign prostatic hypertrophy. In order to further establish the diagnosis of prostatic hypertrophy in the 24 patients (Table 1) we found that 19 (79%) had nocturia more than 2 years before the presenting symptoms of bladder cancer according to the epidemiological interview, 16 (67%) had enlargement of the prostate by intravenous urography before the prostatic surgery and 13 (54%) had enlargement of the prostate by bimanual rectal palpation under general anaesthesia in our department. Although the clinical examinations must be taken with some reservation [2, 7, 12] the majority of the patients had still objective prostatic enlargement, the 13 palpated bimanually in spite of previous prostatectomy.

Only one case-control study demonstrated a significant relationship of bladder cancer with obstructive lesions from prostatic disease especially during the 3 years just before the diagnosis of cancer [4]. It is not possible specifically to exclude, however, that patients who suffer from urinary tract complaints because of cancer in the bladder are more likely than other patients to recall and report prostatic disease and cystitis [4].

Nocturia, which was found significantly more frequently in patients with bladder cancer years before the diagnosis was made, is a non-specific bladder symptom. It could reflect obtruction, infection or bladder cancer itself.

The possible role of infection in the development of bladder cancer was investigated in three previous case-control studies [4, 6, 16]. In the first study an increased risk was found in both men and women but only when infections within the last 5 years before diagnosis of bladder cancer were included [6]. In the two other male studies the duration between the two conditions was not specified [4] or the disease occurred at least 2 years prior to the diagnosis of bladder cancer [16]. Thus, the increased frequency of infection symptoms amongst bladder cancer patients may only be early symptoms of the disease [10]. In a study of female bladder cancer, however, we found no difference between patients and controls concerning a history of bladder infections (dysuria and frequency) when the 2 years diagnosis were disregarded [11].

The present study indicates that persons with a history of venereal disease have an increased risk of developing bladder cancer. The genesis might be immunological or a post gonoccoccal urethral stricture giving rise to bladder obstruction. However, cystoscopy did not show signs of urethral stricture in any patient with a history of venereal disease. Schade and Swinney found in a follow-up study on urethroplasties performed on patients with urethral stricture, that they developed cancer of the bladder six times as frequently as the ordinary population [13]. Thus, urinary obstruction might be important in the development of bladder cancer.

The three urological parameters in the genesis of bladder cancer possibly indicating obstruction have not previously been epidemiologically investigated in a predominantly rural district. The results of the present investigation are supported by two clinical studies.

Fellows reported a significantly higher incidence of infravesical obstruction in 199 male patients with carcinoma of the bladder, than in an age-matched control group. According to radiological signs on intravenous urography the obstruction was defined on the basis of objective parameters such as trabeculation of the bladder, a thick bladder wall, and a large volume of residual urine [5].

In 264 patients with bladder cancer Wallace found that 9% had had a previous prostatectomy for urinary retention, 4% had a prostatectomy at the first planned bladder cancer treatment or during the course of treatment. 2% had bladder diverticula diagnosed at cystoscopy or cystography and 6% had grossly enlarged prostates registered in their medical records. In total, 21% had a history of prostatic hypertrophy or obstructive bladder disease. In 100 cases of carcinoma of the rectum, with the same age distribution and sex ratio, only one case had had an operation of the prostate [15].

Symptoms of prostatic hypertrophy, in our material defined as prostatic enlargement or nocturia, are considered as two pre-disposing factors, but the RR is increased considerably by multiple other factors [8]. It is possible that not only extrinsic factors but also intrinsic factors may be contributing causes, conceivably promoted by prostatic hypertrophy and obstruction.

Before the role of obstructive prostatic hypertrophy in the genesis of bladder cancer can be substantiated, further investigations are needed. This might incorporate further epidemiological and urodynamic studies. Thus, to prove the presence of obstruction one might propose a flow rate measurement and residual urine estimation (e.g. ultrasonic scanning) in bladder cancer patients and age-matched controls.

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