

Case–control study of risk factors for prostate cancer

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Summary One hundred and one patients with histologically confirmed prostate cancer and 202 hospital controls individually matched by age (± 2 years), hospital admittance and place of residence, were interviewed during the period 1990–94 in two towns in central Serbia (Yugoslavia). In an analysis using multivariate logistic regression, the following factors were significantly related to prostate cancer: (1) occupational physical activity during the year preceding the disease [odds ratio (OR)=3.87, 95% confidence interval (95% CI)=2.09–7.16]; (2) occupational exposure to asbestos, steel, dyes and lacquers, bitumen, pitch, iron, nickel, lead, fertilizer and certain other agents (OR=2.13, 95% CI=1.05–4.32); (3) nephrolithiasis (OR=4.52, 95% CI=1.34–15.30); (4) 'other' diseases in medical history such as chronic bronchitis, chronic rheumatic diseases, hypertension, cardiomyopathy, diabetes mellitus, renal diseases, eye diseases and tuberculosis (OR=3.14, 95% CI=1.56–6.33); (5) a greater number (≥ 3) of brothers (OR=2.08, 95% CI=1.35–3.22); and (6) greater numbers (≥ 8) of sexual partners (OR=2.24, 95% CI=1.13–4.44). Marital status, age at first marriage, educational level, age at first sexual intercourse, frequency of sexual intercourse, venereal diseases, tonsillectomy, appendectomy, hernia inguinale and hydrocele, anthropometric characteristics, smoking history, sport and recreational activities and family history of prostatic neoplasms were not found to be independently related to prostate cancer.

Keywords: prostate cancer; epidemiology; risk factors

Prostate cancer is one of the commonest cancers in men, although there are great international and ethnic variations in incidence and mortality (Jensen *et al.*, 1990; Muir *et al.*, 1991). During the period 1969–90 in central Serbia (Yugoslavia), prostate cancer mortality was the fourth highest in rank among all malignant tumours.

Hormonal, sexual, occupational, genetic, dietary and other factors have been suggested as aetiological factors, but relevant epidemiological findings have not been consistent in these respects.

The aim of the present study was to examine several factors that have been suggested to be associated with prostate cancer development.

Materials and methods

Cases consisted of incident prostate cancers diagnosed between January 1990 and December 1994 in two towns in central Serbia (Kragujevac and Cuprija). Out of 141 patients with histologically confirmed clinical prostate cancer, 12 persons could not be interviewed as they gave incorrect addresses, nine patients refused to participate, ten patients could not be interviewed because of their ill-health and nine patients had died. The final group consisted of 101 prostate cancer patients.

For each case two hospital controls were chosen among patients confirmed as having neither prostate cancer nor other prostate diseases. Those with other malignancies were also excluded. All selected controls were interviewed; no one refused to participate. The most frequent diagnosis among the controls were injuries, asthma, pneumonia, peptic ulcer and cholecystitis. Cases and controls were individually matched by age (± 2 years), hospital admittance and place of residence.

During the interview, information was recorded on marital

history, educational and occupational histories, sexual activities, smoking habits, medical history (personal and family) and on some anthropometric characteristics. Data about diet were also collected, but are not reported in this paper. The interviews were usually conducted in the hospital (on admission, after operation or after control examination), but occasionally elsewhere.

In the statistical analysis, univariate and multivariate logistic regression methods were applied. For all calculations an SPSS computer program was used.

Results

One hundred and one patients and 202 controls were matched according to age, hospital admittance and place of residence. The mean age of cases was 70.5 (standard deviation, s.d. 10.46) and 71.50 (s.d. 7.69) for controls. About half the participants (48%) lived in urban areas and half (52%) in rural areas. Both cases and controls had lived over 50 years in their present area of residence.

In the univariate logistic regression analysis, neither marital status nor age at first marriage was associated with prostate cancer. Only one control had never been married, and the mean age at first marriage was about 22 years for all participants. Cases and controls did not differ in educational level or in the main categories of occupation. Significant differences were found for certain occupational exposure (exposure to asbestos, steel, dyes and lacquer, bitumen, pitch, iron, nickel, lead, fertilizer and so on) ($P=0.012$) and for occupational physical activity during the year preceding the disease ($P=0.000$) (Table I). Cases and controls did not differ in their occupational physical activities during the second, third or fifth decades nor in their sport and recreational activities.

Age at first sexual intercourse was similar for cases and controls. Having eight or more sexual partners was reported by 24.9% of cases and 12.9% of controls ($P=0.011$). Having sexual intercourse seven or more times per week was more frequently reported by cases for the third decade (the difference was not significant) and for the fifth decade of their life ($P=0.001$). During the year preceding the disease,

Table I Demographic characteristics of prostate cancer patients and their controls

Variable	Cases (n = 101)		Controls (n = 202)		P-value ^a
	No.	%	No.	%	
Marital status					
Single	–	–	1	0.5	
Married	77	76.2	160	79.2	
Divorced	1	1.0	3	1.5	
Widowed	23	22.8	38	18.8	>0.10
Age at first marriage					
< 20	37	36.6	50	25.2	
20–24	37	36.6	106	52.5	
25–29	21	20.8	33	16.3	
≥30	6	5.9	12	5.9	>0.10
Education (years)					
0–4	59	58.4	131	64.8	
5–12	38	37.6	59	29.2	
> 12	4	4.0	12	5.9	>0.10
Occupation					
Farmers	38	37.6	72	35.6	
Manual workers	45	44.6	101	50.0	
Clerks	18	17.6	29	14.4	>0.10
Specific occupational exposure ^b					
Yes	24	23.8	25	12.4	
No	77	76.2	177	67.6	0.012
Occupational physical activity during the year preceding the disease					
Yes	15	14.9	5	2.5	
No	86	85.1	197	97.5	0.000

^a According to univariate logistic regression analysis. ^b Exposure to asbestos, steel, dyes and lacquer, bitumen, pitch, iron, nickel, lead, fertilizer and so on.

Table II Sexual activity and sexual diseases in prostate cancer patients and their controls

Variable	Cases (n = 101)		Controls (n = 202)		P-value ^a
	No.	%	No.	%	
Age at first sexual intercourse					
< 17	14	13.9	22	10.9	
17–18	30	29.7	59	29.2	
19–20	22	21.8	48	23.8	
≥20	35	34.6	72	35.6	>0.10
Number of sexual partners					
1–7	76	75.1	176	87.1	
≥8	25	24.9	26	12.9	0.011
Frequency of sexual intercourse/week					
At age 20–29					
< 7	68	67.3	151	74.8	
≥7	33	32.7	51	25.2	>0.10
At age 40–49					
< 7	86	85.1	185	91.6	
≥7	15	14.9	17	8.4	0.001
During the year preceding the diagnosis					
0	60	59.4	156	77.2	
≥1	41	40.6	46	22.8	0.002
Gonorrhoea ^b					
Yes	4	4.0	0	0	
No	97	96.0	202	100.0	>0.10

^a According to univariate logistic regression analysis. ^b No other sexual diseases were reported.

40.6% of cases and 22.8% of controls were sexually active ($P=0.002$). Four cases and none of the controls reported gonorrhoea in their medical history ($P>0.10$) (Table II).

The frequency of tonsillectomy, appendectomy, hernia inguinale and hydrocele was similar among cases and controls. None of the participants had had a vasectomy or been circumcised. Cases more frequently reported nephrolithiasis ($P=0.009$) and 'other diseases' ($P=0.000$). Controls had received health checks more frequently than had the case group ($P=0.002$) (Table III).

A higher proportion of cases (20.8%) than controls (8.4%) had body mass index (BMI) ≥ 28 , but the difference was not significant. Participants were also asked about their weight in comparison with their friends during puberty, and during the third and the fifth decade of life. A significant difference between cases and controls was found at age 13–16, cases frequently weighing less than controls ($P=0.005$). There was no significant difference in smoking habits or in the number and type of cigarettes smoked (Table IV). The duration of smoking was similar, as was the age of initiation of smoking

(about 19 years). The number of brothers was significantly greater in cases compared with controls ($P=0.002$). There was no difference in the number of sons.

More cases (17.8%) than controls (4.0%) had family members with prostate cancer ($P=0.002$), this malignant tumour being the most frequent in fathers of both cases and controls (Table V).

All variables that according to univariate analysis were related to prostate cancer at a significant level of ≤ 0.10 were included in the multivariate logistic regression model. According to multivariate analysis the following factors were significantly related to prostate cancer: occupational physical activity during the year preceding the disease, specific occupational exposure, nephrolithiasis, 'other diseases', greater number (≥ 3) of brothers and greater number (≥ 8) of sexual partners (Table VI). Independent significant relationship of these variables with prostate cancer remained after control for dietary factors.

Discussion

Two major hypotheses of prostate cancer aetiology have been suggested: sexual transmission by an infectious agent and hormonal stimulation of prostatic tissue by testosterone. A number of investigations have compared cases and controls with regard to sexual factors (Nomura and Kolonel, 1991). Certain studies found that prostate cancer patients became sexually active at an earlier age (Honda *et al.*, 1988), and had more sexual partners (Krain, 1973; Steel, 1971), had higher frequency of sexual intercourse or venereal disease (Honda *et al.*, 1988; Ross *et al.*, 1987), or a higher fertility (Armenian *et al.*, 1975). In the present study, having eight or more sexual partners showed an association with prostate cancer; only four cases reported a history of venereal disease, but this variable was not independently related to prostate cancer. More sexual partners and a history of venereal disease support the infectious agent hypotheses rather than other components of sexual activity.

Table III Surgical intervention^a, diseases and health control in personal histories of prostate cancer patients and their controls

Variable	Cases (n=101)		Controls (n=202)		P-value ^b
	No.	%	No.	%	
Tonsillectomy	7	6.9	10	5.0	>0.10
Appendectomy	20	19.8	39	19.3	>0.10
Hernia inguinale	23	22.8	33	16.3	>0.10
Hydrocele	2	2.0	1	0.5	>0.10
Nephrolithiasis	10	9.9	5	2.5	0.009
Other diseases ^c	28	27.7	18	8.9	0.000
Health control					
Frequent	39	38.6	116	57.4	
Seldom	62	61.4	86	42.6	0.002

^aNone of the participants had vasectomy or circumcision. ^bAccording to univariate logistic regression analysis. ^cChronic bronchitis, chronic rheumatic diseases, hypertension, cardiomyopathy, diabetes mellitus etc.

Table IV Selected personal characteristics of prostate cancer patients and their controls

Variable	Cases (n=101)		Controls (n=202)		P-value ^a
	No.	%	No.	%	
Body mass index					
<22	22	21.8	33	16.3	
22–27.99	58	57.4	152	75.2	
≥ 28	21	20.8	17	8.4	>0.10
Weight compared with others at age 13–16					
Lower	38	37.6	46	22.8	
Similar	53	52.5	134	66.3	
Higher	10	9.9	22	10.9	0.005
Smoking					
Never	42	41.6	107	53.0	
Former	38	37.6	53	26.2	
Current	21	20.8	42	20.8	≤ 0.10
Number of cigarettes per day (eversmokers)					
≤ 20	47	79.7	69	72.6	
>20	12	20.3	26	27.4	>0.10
Type of cigarettes smoked (eversmokers)					
Without filter					
Yes	52	88.1	80	84.2	
No	7	11.9	15	15.8	>0.10
With filter					
Yes	43	72.9	83	87.4	
No	16	27.1	12	12.6	≤ 0.10
Number of brothers					
0	27	26.6	87	43.1	
1–2	57	56.5	96	47.5	
≥ 3	17	16.9	19	9.4	0.002
Number of sons					
0	14	13.9	60	29.7	
1–2	83	82.2	131	64.9	
≥ 3	4	4.0	11	5.5	>0.10

^aAccording to univariate logistic regression analysis.

Table V Family history of prostate cancer in cases and controls

Affected relative	Cases (n = 101)		Controls (n = 202)		P-value ^a
	No.	%	No.	%	
Father	9	8.9	5	2.5	0.018
Brother	5	5.0	4	2.0	>0.10
Son	2	2.0	–	–	>0.10
Grandfather	2	2.0	–	–	>0.10
Total	18	17.8	8 ^a	4.0	0.002

^aAccording to univariate logistic regression analysis. ^bOne control reported that his father and brother had prostate cancer.

Table VI Risk factors for prostate cancer – multiple logistic regression analysis

Variable	Coefficient	Standard error	P-value	Odds ratio	95% CI
Occupational physical activity during the year preceding the disease	1.3528	0.3142	0.000	3.87	2.09–7.16
Specific occupational exposure	0.7560	0.3606	0.036	2.13	1.05–4.32
Nephrolithiasis	1.5096	0.6214	0.015	4.52	1.34–15.30
'Other' diseases	1.1439	0.3582	0.001	3.14	1.56–6.33
≥3 brothers	0.7341	0.2219	0.000	2.08	1.35–3.22
≥8 sexual partners	0.8049	0.3503	0.022	2.24	1.13–4.44
Constant	-3.0130	0.5235	0.000		

Clinical observation and laboratory experiments have suggested a role for testosterone in the development of prostate cancer. High levels of physical activity may lower testosterone levels, which may reduce prostate cancer risk (Lee *et al.*, 1992). However, epidemiological data on physical activity have not been consistent (Brownson *et al.*, 1991; Paffenbarger *et al.*, 1987). In our study, occupational physical activity during the year preceding the disease was a risk factor for prostate cancer. As adjustment for age did not alter the results, the fact that cases were an average of 1 year younger than the controls could not explain this finding. On the other hand, as controls included patients with asthma, peptic ulcer, cirrhosis and angina pectoris, it is quite possible that the controls were iller than the cases during the previous year and were thus unable to be physically active. This is also in agreement with the fact that the controls had their health checked more frequently than cases. Cases and controls did not differ in their occupational physical activities during the second, third and fifth decades of life. It is clear that occupational activity does not represent complete physical activity, but our cases and controls did not differ in their past sporting and recreational activities throughout their lives.

Several studies have reported a possible connection between prostate cancer and certain occupations, among which three have received the greatest attention: industrial exposure to cadmium, work in the rubber industry and farming (Brownson *et al.*, 1988; Goldsmith, 1980; Williams, 1977). In the present study, certain occupational exposure was a risk factor for prostate cancer but the exposure to a wide variety of agents made it impossible to investigate their separate relevance to this malignant tumour.

In the current study, nephrolithiasis was strongly related to the risk of prostate cancer, La Vecchia *et al.* (1993) also found nephrolithiasis to be more frequently reported by

prostate cancer patients. It is possible that nephrolithiasis helps occurrence and maintenance of some infection which itself is of importance for prostate cancer occurrence.

The findings of an association of prostate cancer with a history of 'other diseases' (chronic bronchitis, chronic rheumatic diseases, hypertension, cardiomyopathy, diabetes mellitus and so on) was unexpected. Which disease or diseases caused this relationship would need to be investigated by looking at a greater number of patients.

Several studies (Steinberg *et al.*, 1990; Spitz *et al.*, 1991) reported a higher rate of prostate cancer in family members of cases than in family members of controls. In our study, the difference in the number of brothers affected by the same malignant tumour could be the result of cases having more brothers than controls, although fathers, grandfathers and sons of cases more frequently had prostate cancer than the same relatives of controls; because the case group was not large enough, this association was not found to be an independent one. We found that having three or more brothers was a risk factor for prostate cancer. However, we did not know whether that fact could be explained by genetic characteristics in the way that a greater number of brothers makes genetic aberrations more likely to happen or, alternatively, the greater number of brothers makes contact with oncogenic agent more likely to occur.

The possibility that relationship between prostate cancer and some factors found in this study is secondary, caused by variables not included in the investigation, cannot be ruled out.

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