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Selected risk factors for transitional cell bladder cancer

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Cancer of the bladder has long been associated with environmental risk factors, such as occupational hazards and smoking. The aim of the current study was to evaluate the contribution of known risk factors on a community basis in the 1990s, in view of the recent worldwide efforts to control environmental hazards. The study population included 140 male patients and 280 matched controls. Information on demographic data, occupational exposure, smoking habits and disease history was obtained by personal interviews. Our study confirmed the role of industrial occupation (OR = 2.21; 95% CI = 1.21–4.02) and exposure to 3 or more metals (OR = 3.65; 95% CI = 1.21–11.08) as risk factors. Prostate enlargement was also found significant, but probably not causal (OR = 2.23; 95% CI = 1.29–3.87). Surprisingly, smoking showed only an inconsistent association with higher rates among those who started to smoke before 18 years of age (OR = 2.64; 95% CI = 1.4–4.99) and those who smoked more than 30 cigarettes per day (OR = 1.82; 95% CI = 0.95–3.49). The above data suggest that current efforts to reduce the load of bladder cancer In the population, via environmental measures, have not as yet yielded significant effects. Medical *Oncology* (2000) 17, 179–182.

Keywords: bladder cancer; smoking; occupational exposure; epidemiology

Introduction

Cancer of the bladder has been one of the first malignant disorders to be related to environmental exposure.[1–3] The three main environmental components identified in the etiology of this disease are occupational hazards,[4] smoking? and, in certain parts of the world, schistomiasis.[6] These risk factors are potentially preventable. Yet, despite the current trend for decreased smoking rates and modern occupational hygiene approach, there has been no parallel decline in the incidence of bladder cancer. Furthermore, in many developed countries, one may even observe an increase.[7,8]

Following is a community study of bladder cancer in Israel, which attempts to delineate current risk factors.

Methods

The study population included all 140 male patients, diagnosed in one supraregional and two regional

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hospitals in central Israel, between 1 July, 1994 and 30 June, 1995. Women were not included due to their small number (28 only).

Two controls, matched to the cases by age (± 5 y), area of birth (classified in 3 groups—Israel, Europe/America and Middle East/North Africa), hospital, and time of admission (within 2 weeks from the respective index case), were selected per case from patients who were hospitalized in the departments of otolaryngology, ophthalmology and orthopedics in the same hospital.

Both cases and controls were interviewed during their first admission. All interviews were conducted via a structured questionnaire, by one of the investigators (DB). It included demographic details, occupational exposure, smoking habits and disease history.

Data analysis

Occupational exposure was assessed using the detailed occupational history reported by the patients. Only exposures over one year in a specific work branch were considered. This information was related to known exposure in the relevant industrial branch according to known data for each occupation.

Smoking of cases and controls was assessed using a number of parameters, as follows: ever smoked, age at start, length of smoking, number of cigarettes per day, packs/year, and length of smoking pause, if relevant. Analysis was performed using an EGRET program designed for matched case-control analysis.[9] The initial list of covariates for multivariate conditional logistic regression analysis included all the variables that were found significant in the univariate analysis and variables that were known to be related to the outcome.

Results

Table 1 presents the distribution of cases and controls by main occupational category and years of education, showing that among the cases there were significantly more industrial workers (OR = 2.29; 95% CI = 1.30–4.02). This observation coincides with the lower level of education of this group (32.9% *vs* 21.5% respectively, grade school education).

Table 2 presents data on previous occupational exposure of the study population to selected industrial agents. A significantly higher exposure among cases, as compared to controls, was observed for nickel,

Table 1 Percent distribution of the study population, Odds Ratio (OR) and 95% CI, by main occupational category and education

Variable	*Cases (n = 140)*	*Controls (n = 280)*	*OR (CI 95%)*
Years of Education			
0–8	32.9	21.5	1.00
9–12	29.3	28.1	0.68 (0.38–1.22)
13+	37.8	50.4	0.49 (0.29–0.84)
Occupation			
Academic/other professionals	36.4	50.0	1.00 –
Secretarial/sales	20.0	16.4	1.67 (0.91–3.07)
Industry	28.6	17.1	2.29 (1.30–4.02)
unknown	15.0	16.4	1.25 (0.65–2.40)
Status of Employment			
Working	46.8	54.5	1.00
Unemployed/ retired	53.2	45.5	1.36 (0.89–2.09)

CI = confidence interval.

Table 2 Percent distribution of the study population, Odds Ratio (OR) and 95% CI, by main occupational exposure

Variable	*Cases (n = 140)*	*Controls (n = 280)*	*OR (CI 95%)*
Nickel			
Not-exposed	91.4	97.5	1.00
Exposed	8.6	2.5	3.66 (1.30–10.55)
Chrome			
Not-exposed	89.3	95.0	1.00
Exposed	10.7	5.0	2.28 (1.04–5.18)
Aluminum			
Not-exposed	90.7	96.1	1.00
Exposed	9.3	3.9	2.50 (1.02–6.19)
Lead			
Not-exposed	90.7	96.1	1.00
Exposed	9.3	3.9	2.50 (1.02–6.19)
Organic solvents			
Not-exposed	85.7	91.4	1.00
Exposed	14.3	8.6	1.78 (0.90–3.49)
Chemical solvents			
Not-exposed	85.7	91.8	1.00
Exposed	14.3	8.2	1.86 (0.94–3.68)
Paint			
Not-exposed	97.9	97.9	1.00
Exposed	2.1	2.1	1.00 (0.20–4.57)
Coal products			
Not-exposed	97.1	96.8	1.00 –
Exposed	2.9	3.2	0.89 (0.23–3.22)
Agriculture chemicals			
Not-exposed	81.4	85.0	1.00 –
Exposed	18.6	15.0	1.29 (0.73–2.29)
Oils			
Not-exposed	95.7	95.7	1.00 –
Exposed	4.3	4.3	1.00 (0.33–2.95)

CI = Confidence interval.

chromates, aluminum and lead (range 8.6–10.7% *vs* 2.5–5.0%, respectively), while a borderline significance was noted in the exposure to chemicals and organic solvents (14.3% *vs* 8.2–8.6% respectively). No difference was noted in exposure to industrial paints.

Table 3 illustrates the association between smoking and bladder cancer. A non-significant OR of 1.31 (95% CI = 0.80–2.15) was noted for ever-smokers as compared to never-smokers. Yet, an increased risk was observed among men who began smoking before the age of 18 y, and for those who smoked more than 30 cigarettes per day (OR = 2.64; 95% CI = 1.4–4.99 and OR = 1.82; 95% CI = 0.95–3.49, respectively). No association with risk was found between the length of smoking, or time since the subjects stopped smoking. This point will be discussed later.

No differences were noted in the distribution of other chronic diseases or repeated urinary infections between the two study groups, but a significant difference of study cases with an enlarged prostate, as reported by the patients, was found (OR = 2.0; 95% CI = 1.23–3.39, data not shown).

Multivariate analysis, presented in Table 4 shows that, except smoking, which did not reach significance, industrial occupation and specifically exposure to heavy metals, as well as enlargement of the prostate remained significant independently of the other factors.

Table 3 Percent distribution of the study population, Odds Ratio (OR) and 95% CI by smoking status

Variable	*Cases (n = 140)*	*Controls (n = 280)*	*OR (CI 95%)*
Status I			
Never smoked	23.7	28.9	1.00
Ever smoked	76.3	71.1	1.31 (0.80–2.15)
Age at start			
Never smoked	23.7	29.6	1.00
Before 18 y	30.2	19.3	2.64 (1.4–4.99)
18 y +	46.1	56.1	1.02 (0.61–1.74)
Length (rears)			
Never smoked	23.7	29.6	1.00
1–19	15.1	16.4	1.11 (0.55–2.50)
20–29	35.9	33.6	1.30 (0.74–2.27)
30 +	22.3	20.4	1.33 (0.70–2.51)
Cigarettes per day			
Never smoked	23.7	29.8	1.00
1–19	23.7	16.9	1.75 (0.92–3.30)
20–29	29.5	38.9	0.94 (0.53–1.67)
30 +	23.0	15.4	1.82 (0.95–3.49)
Packets/year			
Never smoked	25.0	29.6	1.00
0–39	21.3	15.1	1.67 (0.86–3.28)
40–59	27.9	30.6	1.11 (0.61–1.97)
60 +	25.7	24.4	1.26 (0.68–2.31)
Length of smoking pause (rears)			
Never smoked	24.6	29.7	1.00
1–9	11.9	7.9	1.78 (0.78–4.05)
10–19	30.4	22.6	1.63 (0.89–2.96)
20 +	8.7	7.5	1.40 (0.57–3.38)
Current smokers	24.6	32.2	0.92 (0.51–1.68)

CI = Confidence interval.

Discussion

The bladder now constitutes the fourth most frequent cancer site among Israeli males, with an annual age-adjusted incidence rate of 24.7 per 100 000 per year in 1990.[10] The aim of the present study was to examine the effect of known risk factors on a community basis and to evaluate their contribution in the 1990s, following a long period of awareness to the threat of smoking and industrial hazards in the workplace. In contrast with bladder cancer in Egypt, which is primary due to schistomiasis, albeit of the squamous cell variety,[6] industrial pollution, as manifested by smoking and industrial exposure, constitutes the main, possibly even the exclusive, risk factor for bladder cancer in the western world, and has been strongly substantiated in epidemiological and clinical studies?

Table 4 Logistic regression for prediction of bladder cancer

	OR	*(95% CI)*
Metals		
0	1.0	
1–2	0.83	(0.24–2.83)
3	3.65	(1.21–11.02)
Smoking		
Never smoked	1.0	
Ever smoked	1.16	(0.69–1.93)
Prostate enlargement		
No	1.0	
Yes	2.23	(1.29–3.87)
Occupation		
Academic/Professionals	1.0	
Secretarial/Sales	2.06	(1.10–3.86)
Industry	2.21	(1.21–4.02)
unknown	1.27	(0.64–2.54)
Work status		
Working	1.0	
Retired	1.83	(1.03–3.26)

CI = Confidence interval.

Since the early report of Rhen, a German surgeon, who, in 1895, correlated three cases of bladder cancer to work in the paint industry, an increased risk for bladder cancer has been reported continuously in automative, metals, lead, color, gum and oil industries.[1–3] Our results indeed confirm the role of long-term known risk factor of exposure to heavy metals.

Surprisingly, the role of smoking, which has been well established in the etiology of bladder cancer, apparently shows only an inconsistent association in our study, probably reflecting Berkson's bias.[11] This, often disregarded, type of selection bias emphasizes the disadvantage of hospital controls. Since smoking is a strong common risk factor for a large segment of diseases, hospitalized patients will have a higher proportion of smokers as compared to the general population. This issue is discussed more elaborately elsewhere.[12] Still, our results support the findings of numerous other studies that have demonstrated a dose response among heavy smokers,[13–15] as well as a greater risk among people who started to smoke at a young age.

The high risk of prostate enlargement noted in our study may be related to chronic urinary retention which promotes a prolonged contact between urine that contains carcinogenic agents with the bladder cells. However, one cannot rule out a possible confounding effect, stemming from a more frequent examination of the prostate among bladder cancer patients than in the healthy population.

In view of the active measures which have been undertaken to eliminate and/or reduce the exposure of carcinogenic agents, via legislation and otherwise, in industrial countries, one would envisage a decrease in the incidence of bladder cancer in highly developed countries. Unfortunately, this has not, as of yet, materialized. Our study, based on a population diagnosed in the mid-1990s and potentially exposed to environmental hazards 10 to 20 years earlier, a period when antismoking campaigns and occupational legislation were blooming, demonstrates, at least to a certain extent, the futility of these efforts. Alternatively, our data may indicate the presence of a much longer latency period for the development of bladder cancer, stretching back to the 1960s, before the present awareness to the contamination of the human environment became popular. Further efforts should therefore be made to validate our results, in order to present sound data for the reduction of the load of environmental pollution on society.

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