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A Case-control Study of Female Bladder Cancer*

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Abstract—*A case-control study was performed on 47 female bladder cancer patients and 94 female controls matched in age and geographic area. Twenty-five determinants of assumed importance were examined. The bivariate associations revealed a significantly increased relative risk (RR) for bladder cancer associated with use of tobacco, cheroot smoking and saccharin consumption, and some subgroups like never-smokers in combination with use of saccharin. The population attributable risk percentages were estimated. Through a multivariate logistic analysis of selected determinants cheroot consumption was the most pronounced independent variable.*

INTRODUCTION

BLADDER cancer is rarer in women than in men. In Denmark the sex ratio for bladder cancer is estimated to be 3.1–3.2:1 (male:female). The incidence rates in both sexes are reported to be twice as large in the capital than in the rural areas [1]. The incidence rates are slowly increasing in Denmark [1, 2] and in the U.S.A [3], both in men and women. However, the disease is still rather infrequent, particularly in women. Thus the total number of female cases of bladder carcinoma and papilloma in Denmark were 233, 260, 229 and 268 during the years 1973–1976 respectively [1].

In Denmark an epidemiological bladder tumour investigation in a predominantly rural district without any large industries has not previously been performed. As the disease is rare in rural districts, we found it of interest to perform an epidemiological investigation in order to find the most prominent determinants beyond various occupational exposures. The results of a similar investigation considering men is published elsewhere [4]. These results suggested a significantly increased relative risk for bladder cancer associated with the determinants: cigarette smoking, prostatic surgery, nocturia, previous venereal disease, industrial work, work with oil or gasoline and work with various unspecified chemical materials.

No previous bladder tumour investigations in Denmark have revealed any significant risk factors for women. One study in Copenhagen revealed a tendency of increased risk among women who smoked [5]. In our study the questionnaire was designed to ascertain information concerning all the known aspects of bladder cancer aetiology as well as to introduce a search for new features.

MATERIALS AND METHODS

The material comprised 47 consecutive women with newly diagnosed primary bladder cancer (91% with invasive bladder cancer, 96% with transitional cell carcinoma), admitted to the Department of Oncology and Radiotherapy, Aarhus Municipal Hospital from September 1977 to July 1980. The average age was 66.4 yr (range 44–83 yr). The department receives patients from a well-defined geographic area with about 1.5 million inhabitants. The residence of the patients by degree of urbanization appears in Table 1. The controls had an identical distribution. A questionnaire was followed by an interview at the hospital carried out by the same physician (SM). The questions appear in Table 2.

The patients were matched to controls through the regional division of the national register on a one-to-two basis, not only in respect to sex and age but also to geographic area, including degree of urbanization. A questionnaire was sent to all

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Table 1. Distribution of residence for 47 female patients with bladder cancer and the corresponding 94 controls

Residence	%
Rural district:	
farm	13
village (<1000 inhabitants)	23
smaller town (1000–10,000 inhabitants)	30
Larger town (10,000–100,000 inhabitants)	19
City (>100,000 inhabitants)	15
Total	100

Table 2. Questions used in the female bladder cancer aetiology study

Socioeconomic level
Type of work
Work with chemical materials
Occupational history
Alcohol-drinking habits
Smoking habits
Coffee-drinking habits
Use of artificial sweeteners as a sugar substitute
Drug treatment
Family history
Previous and present diseases of the urinary tract
Previous and present diseases of the lungs
Chronic diseases

controls. Non-response was followed by a second mailing, and persistent non-response by a third mailing. After we had received the completed questionnaires all the controls were interviewed by telephone by the same physician. The procedure is described in detail elsewhere [4].

The material was processed at the regional computer centre and a linear logistic multivariate regression analysis was used. 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. The statistical procedure is described in detail elsewhere [4].

RESULTS

The selection and the response percentages for the controls appear in Table 3. Eighty-one per cent of the first selected controls responded to the questionnaire and 54% responded at first contact.

In Table 4 the bivariate associations of selected determinants for bladder cancer are shown. The relative risk (RR) was estimated through the cross-product ratio. The confidence limits were based on the χ^2 test from the differences between the basis value and the values of the independent variables [6]. The population attributable risk

Table 3. Selection and reply for 94 female controls matched to 47 female patients with urinary bladder cancer

Selected control persons	Primary answer No.	%	Secondary answer No.	%	Tertiary answer No.	%	All answers No.	%
First selected	51	54	14	15	11	12	76	81
First substitute	8	9	4	4	2	2	14	15
Second substitute	4	4					4	4
All controls	63	67	18	19	13	14	94	100

Table 4. The bivariate associations expressed as the relative risk (RR) and the population attributable risk percentage (AP) of selected determinants for bladder cancer among 47 female patients and the corresponding 94 controls

Independent variable	No. of cases	No. of controls	G^2 (d.f. = 1)	RR*	AP†
Cheroot smoker	11	8	5.6	3.3 (1.2– 8.8)	16.3
Saccharin consumption	6	2	6.2	6.7 (1.5–30.2)	10.9
Cigarette smoker	22	30	3.0	1.9 (0.9– 3.9)	21.9
Use of oestrogen	3	1	3.0	6.3 (0.8–51.3)	5.4
Work in industry	4	3	1.8	2.8 (0.6–13.1)	5.5
Coffee consumption	46	89	0.9	2.6 (0.4–18.8)	60.0
Work with chemical materials	6	5	2.3	2.6 (0.8– 9.0)	7.9
Cigarette or cheroot smoker	27	35	5.2	2.3 (1.1– 4.6)	32.2

*Estimated from cross-product ratio with 95% confidence limits.
†Only meaningful in significant associations.

Table 5. Logistic regression analysis: the relative risk (RR) for women calculated from 7 selected determinants by 47 female bladder cancer patients and 94 controls

Independent variable	RR	RR	RR	RR	RR	RR	RR	RR
Basis*								0.50
1 Cheroot smoker	3.21	3.14	3.07	2.89	2.99	3.15	3.28	
2 Saccharin consumption	7.52	8.17	7.24	7.81	7.38	6.36	—	
3 Cigarette smoker	1.72	1.81	1.91	1.94	1.97	—		
4 Use of oestrogen	4.49	4.97	5.06	6.24	—			
5 Work in industry	2.38	2.33	2.41	—				
6 Coffee consumption	3.57	3.74	—					
7 Work with chemical materials	1.73	—						
Excluding independent variable	none	7	6	5	4	3	2	
G^2 values†	159.69	160.27	161.34	162.42	165.24	168.35	173.88	179.50
Degrees of freedom (d.f.)	133	134	135	136	137	138	139	140
ΔG^2‡ (d.f. = 1)	0.58	1.07	1.08	2.82	3.11	5.53	5.62	
P values	NS	NS	NS	NS	NS	<0.025	<0.025	

Dependent variable: risk for bladder cancer by women.
*Basis = probability of bladder cancer/probability of non-bladder cancer.
†$G^2 = \chi^2$ for great values.
‡ΔG^2 = differences between G^2 values.

percentage (AP) was estimated according to the method of Cole and MacMahon [7]. The AP percentages are only meaningfully interpretable in significant associations.

In Table 5 a multivariate logistic regression analysis of 7 discriminating variables which were dichotomised (yes/no) is seen. The RRs 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 cheroot smoking. The RR of developing bladder cancer for women smoking cheroots was 3.28 times greater than for women who were non-cheroot smokers. This increment in RR was significantly different from the basis value ($\Delta G^2 = 179.50 - 173.88 = 5.62$, d.f. = 140 - 139 = 1, $P < 0.025$). The RR was increased to 20.03 (3.15×6.36) if they were both cheroot smokers and used saccharin in coffee or tea. The increased risk from 3.28 to 20.03 was statistically significant ($\Delta G^2 = 173.88 - 168.35 = 5.53$, d.f. = 139 - 138 = 1, $P < 0.025$).

Table 6 shows the results for some of our subgroups which have been described in the literature to be of importance in the development of bladder cancer. Within the table the G^2 was calculated from the product of the independent relative risks of the two variables in question, whereas the RR reflects the bivariate associations of the subgroups.

The distribution of the 3 most pronounced determinants was independent of age groups and degree of urbanization, so a stratified analysis was not performed and the matching variables were not applied as independent variables in the logistic regression analysis, due both to the small size of the material and to the frequency of events.

Table 6. The relative risk (RR) for some subgroups calculated by 47 female bladder cancer patients and 94 controls

Independent variable	G^2 (d.f. = 2)	RR*
Never-smokers and saccharin users	11.5	3.3 (1.4- 7.8)
Never-smokers and coffee drinkers	5.1	1.0
Cigarette and cheroot smokers	8.0	5.6 (1.3-24.8)

*Estimated from the cross-product ratio with 95% confidence limits in the significant associations.

A tendency toward increased RR for bladder cancer with increased daily consumption of current cigarettes and/or cheroots was found, though not at a significant level. By application of *lifetime* consumption of cigarettes or cheroots (No. daily × No. of years) a significant trend was found by means of a linear bivariate regression analysis (cigarettes: $y = 0.7378x + 0.7106$, $r = 0.8159$; cheroots: $y = 0.7571x + 0.4642$, $r = 0.8557$).

DISCUSSION

In female bladder tumour investigations only cigarette smoking has been revealed as a significant risk factor in the development of the disease [8–13]. Coffee consumption or use of artificial sweeteners have not been referred to as significant risks, but some subgroups have been suggested as being of importance [9, 10, 14–17].

In studies of this kind some biases must be taken into account [18]. Further, owing to practical and economical limitations, information in this study

was not obtained in exactly the same fashion from the patients and the controls, i.e. personal interviews vs telephone interviews after we had received the questionnaires. These differences, however, are assumed not to influence the reliability of the response to the determinants in question.

In our study we have observed a significant association between cheroot smoking and bladder cancer in women for the first time. In the study of Lockwood [5], with a total of 87 female patients and 87 female controls, there were 26 patients vs 19 controls smoking cigars or cigarillos, and there were 12 patients and 11 controls preferring cigarettes, i.e. there were no significant differences. In our material there were more cigarette smokers than cheroot smokers, but only a significant association to cheroot smokers was found. Today it is probably more common for women to smoke cigarettes than cheroots, which might explain the difference in smoking habits between the two studies. It is also possible that women in urban areas are more commonly cheroot smokers than cigarette smokers compared to women in rural areas. However, this cannot explain the significant difference in our study between the patients and controls smoking cheroots. It is shown by the Ames test that cigarette smokers have mutagenic urine while non-cigarette smokers do not [19]. The same might underlie female cheroot smokers and so explain the increased RR in developing bladder tumours. This might also be supported by the increased RR for patients smoking cigarettes and/or cheroots (Tables 5 and 6).

The *lifetime* consumption of cigarette and cheroot smoking was significantly related to the increased RR. The *current* smoking habits of cigarettes and cheroots, however, did not reveal a significant association in the dose–response relationship, presumably caused by the size of the material.

Some studies have revealed a risk to females associated with coffee consumption, but only in such subgroups as those who drink more than one cup a day [14], urban dwellers [10] or instant-coffee drinkers with a lifetime consumption of more than 10,000 cups [9]. In our study there was no significant association with coffee consumption. We were also unable to demonstrate an increased risk in the subgroup of coffee drinkers who are never-smokers [14].

Since a Canadian epidemiological study showed a relationship between saccharin consumption and bladder cancer [20] other studies have not been able to replicate these results [16, 17, 21]. A significantly excessive risk for saccharin has been found in non-smoking women after an age-stratified analysis [16] and in never-smoking women who had not been in a risk occupation [17]. However, another study does not reveal these risks for women but only for men [13]. Our study, concerning saccharin as a sugar substitute, supports this subgroup's increased risk (Table 6). Further, we found a significantly excessive RR in women using saccharin alone. However, the estimates are based on relatively small numbers and are subject to large statistical fluctuations.

We did not find any differences or tendencies in the other investigated parameters (Table 2). In contrast to our male study [4], we did not find any differences concerning the symptoms of cystitis. There were 8 patients and 13 control persons with a previous history of dysuria (at least 2 yr before presenting symptoms of bladder cancer).

Because of the small size of the material our findings only etablished statistically significant differences between cases and controls in the smoking of cheroots, saccharin consumption and some subgroups. However, if possible, a greater non-occupational female case-control study from a rural district is desirable. In Denmark we have only about 90 female bladder tumour patients per year outside the capital, and still fewer outside the cities. Thus a multicentre investigation would be necessary for a further demonstration of non-occupational risk factors in the development of bladder cancer in females.

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