

The Copenhagen case-control study of bladder cancer: role of smoking in invasive and non-invasive bladder tumours

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SUMMARY A population based study of 388 cases of bladder cancer including papillomas and 787 controls in Greater Copenhagen confirmed the role of smoking in the aetiology of bladder cancer. Significantly increased relative risks were found for persons who had smoked only cigarettes (RR = 2.9; both sexes combined) and for mixed smokers including cigarettes (RR = 3.6; both sexes combined). Multiple logistic regression analysis showed significant influences of the amount (pack years) of cigarettes smoked and a reduced risk among persons who had stopped smoking. No significant effects of smoking pipe or cigars/cigarillos were apparent, and the present study does not confirm previous suggestions of associations between the smoking of cigars/cigarillos and bladder cancer in Denmark. Only a slight increase in relative risk with the amount smoked was found. The influence of smoking on bladder cancer risk was similar for tumours in stages T₁ and T₂₋₄ at diagnosis and also for tumours of grades 1-2 and grades 3-4 at diagnosis.

Clemmesen and Nielsen¹ suggested in the 1950s that the observed increase in the incidence of bladder cancer (including papilloma) in Copenhagen was due to tobacco smoking. Case-control studies in the second half of the 1950s confirmed the role of smoking. In Copenhagen, Lockwood² found a clear association between bladder cancer and smoking in particular cigarettes. These early observations supported the finding of bladder tumours in mice after exposure to tobacco tar,³ and numerous studies have reported an increased risk of bladder cancer in humans in relation to smoking, as reviewed by Matanoski.⁴

While the association with cigarette smoking seems clear, the role of other types of tobacco, for example cigars and pipes, has not yet been clarified, though it has recently been suggested that cigar smoking is associated with a 3 to 4-fold risk of bladder cancer in Danish women.⁵ The diversity of smoking in Denmark makes it possible to investigate the role of various smoking habits in bladder carcinogenesis.

The aetiology of invasive and non-invasive tumours of the lower urinary tract is in general regarded as identical, and papilloma and frankly invasive tumours of the bladder are often considered together since the

distinction between them is difficult and papillomas are assumed invariably to show invasive growth if left untreated. Aetiological research distinguishing between invasive and non-invasive tumours has rarely been carried out, but it was suggested recently that the aetiological role of cigarette smoking is largely confined to non-invasive bladder tumours.⁶

Here we report on the association between various types of tobacco smoking and bladder cancer in Copenhagen and include an examination of the relation to tumours of various grades⁷ and T-stages.⁸

Material and methods

CASES

The investigation includes tumours located in the urinary bladder only. As the clinical distinction between non-invasive (papilloma) and invasive tumours of the urinary bladder is difficult,⁹ they are grouped together as "bladder cancer".

Ascertainment of cases and controls for the study and the interviewing techniques have been described in detail elsewhere.¹⁰ From May 1979 to April 1981, a total of 412 patients living in the municipalities of

Table 1 Percentage distribution of cases of bladder cancer in Copenhagen case-control study 1979-81 by histological type and T stage

Bladder cancer characteristic	Men (age, years)			Women (age, years)		
	- 54	55-64	65 +	- 54	55-64	65 +
Number of cases	46 (100.0%)	107 (100.0%)	137 (100.0%)	16 (100.0%)	33 (100.0%)	49 (100.0%)
Transitional cell tumour, total	93.4	87.8	86.1	87.5	97.0	83.7
Grade 0-2	71.7	60.7	54.0	50.0	66.7	59.2
Grade 3-4	21.7	27.1	32.1	37.5	30.3	24.5
Squamous cell and solid tumours	2.2	3.7	8.0	6.3	0.0	10.2
Other	4.3	8.4	5.8	6.3	3.0	6.1
Tumour stage, TA	33.3	34.3	33.8	35.7	48.3	29.2
T0-1	33.3	31.4	33.8	28.6	31.0	27.1
T2	11.9	7.6	9.0	14.3	3.4	6.3
T3	7.1	11.4	14.3	7.1	6.9	18.8
T4	2.4	4.8	1.5	7.1	0.0	8.3
Unclassified	12.0	10.5	7.6	7.2	10.4	10.3

Copenhagen and Frederiksberg and the county of Copenhagen were referred to the study, and 389 of these (94.4%) were interviewed. A comparison with the records of the Cancer Registry for the population and time period in question shows the case group to be a representative sample of all bladder cancer cases arising in Greater Copenhagen with regard to age, sex, place of residence by area, and occupation.

Some 99% of the male and all of the female bladder tumours were histologically verified; 89.4% of all tumours were of the transitional cell type, of which 66.6% were Bergquist grades 0 to 2.⁷ A total of 61.2% of patients had tumours in stages TA without infiltration or T1 with infiltration of subepithelial connective tissue only; 3.6% were T4 tumours, that is, with fixation. The majority of cases were thus investigated in early stages of the disease. Details of the histological grading and T-staging of the tumours is given in table 1.

CONTROLS

Controls were selected at random in April 1979 among the residents of the municipalities where the cases were living. The sample was stratified to group match the cases with regard to sex and five-year age groups. As all controls were drawn at the beginning of the study, some had died or moved out of the area when approached for interview during the following two years. Such controls were replaced by drawing new persons at random from the list of residents in the same age and sex groups. Among 1052 controls approached, the overall participation rate was 75.1%, as described previously.¹⁰

INTERVIEWS

Interviews were usually conducted in the individuals'

homes by trained interviewers, who used a structured questionnaire to obtain information on known or suspected risk factors for bladder cancer. Included were questions on tobacco smoking, drinking of coffee, tea, and other beverages, use of artificial sweeteners, use of drugs, other medical procedures, previous medical conditions, and occupation.

A smoker was defined as a person who had "ever smoked one cigarette, pipe or cigar daily for as long as three months". If a smoker had regularly smoked cigarettes, pipe, cigars, or cigarillos, he/she was asked the age when he/she had started and the age when he/she had stopped smoking a particular type of tobacco.

STATISTICAL ANALYSIS

The statistical analysis of this unmatched case-control study was done by unconditional maximum likelihood estimation of the parameters of a logistic regression model¹¹ using the GLIM package.¹² The consumption of cigarettes, pipe tobacco, cigars, and cigarillos was calculated as pack-years or pack-year equivalents, ie, 20 g (1 pack of cigarettes) tobacco smoked per day in one year. One cigar was counted as 5 g tobacco and 1 cigarillo (or cheroot) as 3 g tobacco, while pipe tobacco was measured directly as quantity consumed per week. The continuous variable for cigarettes was categorised into three different levels to derive category specific relative risk (RR) estimates.

In addition to analysing the data from all cases of bladder cancer, relative risks were also estimated from a logistic regression model in which cases with transitional cell tumours grades 0-2 or 3-4 were compared separately with all controls. Similarly, the relative risks were calculated for development of tumours of stages TA-T1 or tumours of TW-T4 (table

1). For the logistic regression modelling, the maximum number of individuals with complete information on the variables of interest was used.

Results

Table 2 shows that approximately 90% of the adult male and 70% of the adult female population in

Table 2 Smoking habits in Copenhagen 1979–81, based on information from population controls

Characteristic	Men	Women
No of controls	592	195
Ever smoked regularly	88.5%	66.7%
– 54 years	89.4%	67.9%
55–64 years	89.2%	74.2%
65+ years	87.7%	60.0%
Ever cigarettes only	21.1%	44.6%
Ever pipe only	3.0%	0.0%
Ever cigars or cigarillos only	4.1%	9.2%
Mixed, with cigarettes ever	51.0%	12.3%
Mixed, without cigarettes	9.3%	0.5%

Table 3 Estimates* of relative risk for bladder cancer for different types of smokers, Copenhagen 1979–81

Smoking category	Cases	Controls	RR	95% CI
Non-smoker	26	132	1.0	—
Cigarettes only	115	210	2.9	(1.8–4.8)
Pipe only	6	18	1.9	(0.7–5.4)
Cigar only	1	2	2.5	(0.2–28.40)
Cigarillos	8	39	1.0	(0.4–2.4)
Mixed smoker, including cigarettes	197	315	3.6	(2.2–5.8)
Mixed smoker, excluding cigarettes	18	55	1.9	(0.9–3.8)

* Adjusted for age and sex

Table 4 Parameter estimates in multiple logistic regression analysis of bladder cancer with smoking related variables, Copenhagen 1979–81

Model	Deviance	DF	Ever smoked	Stopped smoking	Log pack-year or equivalents		
					Cigarettes	Pipe	Cigars/cigarillos
1	1398	1136	1.218 ^c (+/-0.235)	-0.542 ^c (+/-0.153)			
2	1385	1135	0.623 ^a (+/-0.291)	-0.478 ^b (+/-0.155)	0.088 ^c (+/-0.025)		
3	1397	1137			0.120 ^c (+/-0.020)		
4	1382	1133	0.490 (+/-0.322)	-0.451 ^b (+/-0.156)	0.095 ^c (+/-0.027)	0.037 (+/-0.021)	0.002 (+/-0.027)
5	1391	1135			0.121 ^c (+/-0.020)	0.047 ^a (+/-0.021)	0.012 (+/-0.019)
6	1382	1132	M 0.996 ^a (+/-0.411) F 0.018 (+/-0.556)	0.529 ^b (+/-0.173) -0.214 (+/-0.362)	0.082 ^b (+/-0.027) 0.127 (+/-0.063)		

^a p<0.05, ^b p<0.01, ^c p<0.001

Copenhagen had been regular smokers at some time before the interview. No major differences are seen between age groups except possibly for a lower proportion of smokers among women aged 65 years or more. Some 60% of the male population controls have smoked different types of tobacco regularly, but 70% have been regular smokers of cigarettes either alone or in combination with other tobacco. Almost 60% of the women have smoked cigarettes regularly.

Smokers of various categories have in general a significantly increased risk of bladder cancer compared with non-smokers. Table 3 shows for the two sexes combined that significantly increased risks are associated with the smoking of cigarettes either alone (RR = 2.9) or in combination with other types of tobacco (RR = 3.6).

The corresponding estimates of relative risk for men and women separately are for smokers of cigarettes alone: men RR = 4.0 (95% CI = 1.9–8.6) and women RR = 2.3 (95% CI = 1.2–4.3). For mixed smokers including cigarettes, men RR = 4.6 (95% CI = 2.2–9.5) and women RR = 3.1 (95% CI = 1.4–7.1). Non-significant increased risks are also noted for pure pipe smokers (RR = 1.9) and for mixed smokers who had never smoked cigarettes (RR = 1.9). The relative risk associated with ever smoking cigarettes is 2.5 (95% CI = 1.8–3.5), for ever smoking cigars or cigarillos 1.0 (95% CI = 0.8–1.3), and for ever smoking pipe tobacco 1.4 (95% CI = 1.0–1.8). As numbers are small and as the type of tobacco is identical, smoking of cigars and cigarillos has subsequently been considered jointly.

Table 4 shows the estimated regression coefficients of ever smoked (1 = yes, 0 = no), stopped smoking (1 = yes, 0 = no), and the continuous variables of pack

The Copenhagen case-control study of bladder cancer

years or pack year equivalents, with a logarithmic transformation with a value for never smoked defined as log 0.01. For each model the deviance is given with the degrees of freedom, and this allows one to assess whether insertion or deletion of a variable affects the goodness of fit significantly.

Smokers have a significantly increased risk of bladder cancer (model 1) with RR 3.4 (men: RR = 4.7; women: RR = 2.5), while those who have stopped smoking have a significantly reduced risk (RR = 0.6) compared with current smokers (men: RR = 0.6; women: RR = 0.6). The amount of cigarettes smoked (pack-years) has a significant influence on the fit of the model (model 2) as its inclusion leads to a substantial reduction in the effect of ever smoking. Pack-years alone can reduce the deviance by 39 with one degree of freedom, and it is thus a highly significant determinant of bladder cancer risk (model 3). Accounting for the amounts of cigars/cigarillos and pipe tobacco smoked does not improve the fit of the model significantly (model 4), although pipe smoking has a marginally significant effect (model 5). The effect of cigar/cigarillos smoking is not significant.

Risk of bladder cancer is thus adequately determined by age, sex, ever smoked, stopped

smoking, and amount of cigarettes smoked, which are included in model 2. Model 6 shows that the effects are in the same direction for both sexes but that the effect of ever smoking is particularly strong in men while pack-years of cigarettes is the strongest determinant in women.

The relative risks for categories of pack-years of cigarettes are all statistically significant (table 5). The major part of the increase in the relative risk is determined by the transition from non-smoking to ever smoking cigarettes, with a very slight increase in risk with the amount smoked.

The association between smoking and bladder tumours of different grades according to Bergquist's classification or T-stages at the time of diagnosis is given in table 6. When a comparison is made with smoking habits in the total group of controls, it is seen that the association with smoking is virtually identical for the various subcategories of bladder tumours. In the models, considering simultaneously the effect on bladder cancer risk of ever smoked, stopped smoking, and log of pack-years of cigarettes, there is an approximately twofold risk associated with ever smoked, a reduction in risk to about 0.6 by stopped smoking, and a relative risk of 1.1 per pack-year, irrespective of grade or stage of the tumour.

Table 5 *Relative risk of bladder cancer in Copenhagen 1979-81 in relation to amount of cigarettes ever smoked*

Amount of cigarettes smoked		Cases; controls	RR*	95% CI
Pack-years	1000 cigs			
0	0	61;253	1.0	—
1-19	-146	101;188	2.4	(1.6-3.5)
20-39	-292	98;167	2.6	(1.8-3.8)
40+	292+	111;163	2.9	(2.0-4.3)

*Adjusted for age and sex

Discussion

The well established association between smoking and bladder cancer is also present in this population based case-control study in Greater Copenhagen. The increased risk is in particular associated with cigarettes whether smoked as the sole source of tobacco or in combination with other types of tobacco among mixed smokers (table 3). The significantly increased risk is seen in both men and women (table 4). The results are

Table 6 *Smoking and relative risk for subgroups of bladder cancer including papilloma in Copenhagen 1978-81, men and women combined*

Bladder cancer category	Number of cases ^c	Smoking variable					
		Ever smoked		Stopped smoking		Amount cigarettes (log pack years)	
		Regr coeff	RR	Regr coeff	RR	Regr coeff	RR
Total	371	0.62 ^a (+/-0.29)	1.9	-0.48 ^b (+/-0.16)	0.6	0.09 ^b (+/-0.03)	1.1
Transitional cell carcinoma, grades 0-2	222	0.57 (+/-0.35)	1.8	-0.49 ^b (+/-0.19)	0.6	0.08 ^b (+/-0.03)	1.1
Transitional cell carcinoma, grades 3-4	104	0.64 (+/-0.54)	1.9	-0.37 (+/-0.25)	0.7	0.11 ^b (+/-0.04)	1.1
Stage TA-T1	246	0.77 ^a (+/-0.36)	2.2	0.61 ^b (+/-0.19)	0.5	0.09 ^b (+/-0.03)	1.1
Stage T2-T4	90	0.60 (+/-0.49)	1.8	0.42 (+/-0.27)	0.7	0.06 (+/-0.04)	1.1

^a p<0.05 ^b p<0.01 ^c Number of controls = 771 in all analyses

in line with recent investigations from Europe, North America, and Japan.^{13 20} The relative risk estimate is slightly higher than that emerging from most other studies in the United Kingdom, the United States, and Canada, but of the same order of magnitude as in previous studies in Denmark¹⁸ and Italy.²⁰

Both tables 4 and 5 indicate that there is an increase in risk with increasing amount of cigarettes smoked, although the dose response relation is less strong and consistent than is seen for other smoking related cancer, for example, lung, laryngeal, and oesophageal cancers.

The dose response relation also seems less strong in the present study than in a recently reported study from Italy²⁰ but more like the uneven patterns described in the United States¹³ and England.¹⁹ No exact information has been obtainable from the cigarette manufacturers on the composition of Danish cigarettes, but they consist mainly of flue-cured blond tobacco (Virginia tobacco) with the admixture of air-cured black tobacco for certain brands.

The aetiological role of pipe tobacco or cigars in bladder cancer is not clear. Tables 3 and 4 indicate that pipe smoking increases the risk, although it is of borderline significance (table 4). There was also an indication of an increased risk associated with pipe smoking in the study performed in Copenhagen by Lockwood between 1956 and 1958, and a risk of 1.6 relative to the risk in non-smokers can be calculated from the data reported.² By contrast, a study carried out between 1977 and 1980 showed no association with pipe smoking in Danish rural districts and provincial towns.¹⁸ A case-control study from Canada has also provided suggestive evidence that pipe smoking increases the risk of bladder cancer.¹⁵

Three case-control studies of bladder cancer in Denmark have examined the association with tobacco (table 7). In the case-control study performed in Copenhagen 20 years before the present study, Lockwood reported an association with heavy cigar or

cigarillo smoking.² A relative risk of 1.1 can be calculated from the data published, but there is a statistically significant increased risk (RR=3.2) among men smoking 31g or more of cigars or cigarillos per day, equivalent to approximately seven or more cigars per day. No dose-response relation is, however, present. In spite of a substantial number of cigar smoking women for whom an overall RR of 1.6 can be calculated, no dose-response relation is seen for that sex, nor is there an increased risk associated with heavy cigar smoking among women. By contrast, Mommsen and Aagaard⁵ recently reported an increased risk of bladder cancer among cigar and cigarillo smoking women in a case-control study drawing cases and controls from provincial towns and rural districts in Denmark, but no association was seen in men.¹⁸ Neither of these previous findings from Denmark was confirmed by the present study, which showed no association with cigar or cigarillo smoking (tables 3 and 4) in either men or women when other smoking habits were taken into account. The role of cigar and cigarillo smoking has not been investigated elsewhere in the world.

It has been suggested that cigarette smoking as an aetiological factor is largely confined to non-invasive bladder tumours.⁶ Approximately 90% of the bladder tumours included in the present study have been classified with regard to clinical T-stage at the time of diagnosis (table 1). For 65-70% of the cases with no substantial differences between age groups and sexes there is no clinical sign of invasion at the time of diagnosis (TA-T1), while 20-30% of the cases show invasive growth or spread beyond the bladder wall. There is no indication from the present study that the risks associated with smoking are different for tumours that are less (TA-1) or more (T2-4) aggressive.

Some 90% of the tumours in both sexes and age groups are transitional cell carcinomas, which have been classified according to epithelial differentiation

Table 7 Relative risk of bladder cancer associated with smoking in three Danish case-control studies (smokers v non-smokers)

Year	Lockwood, 1961 ²⁺		Mommsen, 1985 ^{5 18}		Present study	
	Copenhagen		Rural & provincial towns	Copenhagen	M	F
Population covered	M	F	M	F	M	F
Sex	282;282	87;87	165;165	47;94	290;592	98;195
N of cases; controls						
Cigarettes only	2.7*	3.3	3.5*	3.2*	4.0*	2.3*
Pipe only	1.6	—	6.2*	—	1.9	—
Cigars/cigarillos only	1.1	1.6	2.3	—	1.3	1.3
Mixed including cigarettes	3.7*	—	7.8*	2.8	4.6*	3.1*

* RR significantly increased, p < 0.05

+ RR calculated from author's data

‡ Includes prevalent cases from 1943 and later.

The Copenhagen case-control study of bladder cancer

at the time of diagnosis. If grades 3 and 4 are regarded as more "aggressive" than grades 0-2, there is no difference in smoking associated relative risk with aggressiveness measured by the degree of differentiation of the tumour (table 6). These results are in line with the results of Lockwood, who found no difference in smoking habits among papilloma patients and patients with invasive bladder tumours.²

In conclusion, the present study corroborates the association between smoking and bladder cancer. In both sexes, smoking is the most important determinant of bladder cancer in the present study in which the role of artificial sweeteners, coffee, tea, and beverages, and selected occupations have been reported elsewhere.^{10 21 22} In line with previous investigations, there is a suggestion that pipe smoking increases the risk, while previous reports of bladder cancer in relation to smoking of cigars have not been confirmed. The regression coefficient for the models including pack-years or pack-year equivalents, eg, model 5, can be used to estimate the relative bladder cancer risk of persons with various smoking histories. Someone who smokes, for example, one pack (20 cigarettes) daily for 40 years has a 2.7 times higher risk of bladder cancer than a non-smoker calculated as $((40/0.01) \cdot 0.12 = 2.7)$. The similar relative risk for a pipe smoker who has smoked for 40 years is 1.5. Table 2 shows that 89% of all male controls have been regular smokers. Based on this proportion and the weighted relative risks, it can be calculated that the population attributable risk for smoking²³ is 73% among men and 48% among women. This means that some 350 new bladder cancers out of the total number of 420 presently diagnosed in Copenhagen every year²⁴ are potentially preventable by cessation of smoking. The present results give a clear indication that cessation of smoking is indeed associated with a decreased risk of bladder cancer development in individuals.

We thank the following hospital departments which reported their patients to the study: Bispebjerg, Department of Surgery D; Hvidovre, Department of Urology; Herlev, Department of Urology; Glostrup, Department of Surgery A; Gentofte, Department of Surgery; Rigshospitalet, Department of Surgery D; Diakonissestiftelsen, Department of Surgery; Sct Lukasstiftelsen, Department of Surgery; Frederiksberg, Department of Surgery K; Sundby, Department of Surgery; Finsen Institute; Sct Elisabeth, Department of Surgery.

Interviews were carried out by Ms H Nøjed and Ms U Larsen. Ms Aa Larsen provided technical assistance with data editing and analysis. Mr G P Sorber assisted with programming, and Ms Aa Falck and Ms M Harnek with preparation of the manuscript. This

project was supported by the US National Bladder Cancer Project (Grant No. CA-24119) and by Købmand Peter Bernhard Rasmussen's Foundation.

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Congress of the European Committee for Therapeutic Research in Multiple Sclerosis

3–5 September 1987, Lyon, France.

“Trends in European Multiple Sclerosis Research”.

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