Exhibit 263

THE COPENHAGEN CASE-CONTROL STUDY OF RENAL PELVIS AND URETER CANCER: ROLE OF SMOKING AND OCCUPATIONAL EXPOSURES

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Smoking habits and occupational exposures were investigated for 96 patients with cancer of the renal pelvis and ureter (including papilloma) and 294 hospital controls. In comparison with persons who never smoked, significantly increased relative risks were seen for smokers of cigarettes alone (RR = 2.6; 95% CI: 1.0–6.7) and in combination with other types of tobacco (RR = 3.8; 95% CI: 1.3–11.5). Non-significantly increased relative risks were observed for pipe smokers (RR = 2.2; 95% CI: 0.1–97) and for mixed pipe, cigar, and cigarillo smokers (RR = 6.5; 95% CI: 0.4–21.2). A strong dose-effect ($p < 0.001$) relationship was seen between the lifetime total amount of tobacco smoked and the risk of pelvis-ureter tumors, with the heaviest smokers having an 8-fold risk. Comparison with the dose-effect relationship for a parallel study of bladder cancer indicated that the relationship with tobacco was stronger for pelvis-ureter tumors. Deep inhalation of cigarette smoke increased the risk (RR = 3.4; 95% CI: 1.9–6.1), while stopping smoking (RR = 0.6; 95% CI: 0.3–1.1) and use of filter cigarettes (RR = 0.5; 95% CI: 0.3–0.9) decreased the risk. Significantly increased risks emerged for employment in the chemical, petrochemical and plastics industries (RR = 4.0; 95% CI: 1.6–9.8), and for exposure to coal and coke (RR = 4.0; 95% CI: 1.2–13.6), asphalt and tar (RR = 5.5; 95% CI: 1.6–19.6). Cigarette smoking accounted for 56% of male and 40% of female pelvis and ureter tumors in eastern Denmark.

Cancer of the renal pelvis and ureter are rare, accounting for approximately 3.5% of all kidney and urinary tract tumors in Denmark (data not shown). Tumors of these sites have attracted relatively little attention and they are assumed to share risk factors with bladder tumors (Morrison and Cole, 1982). In Denmark, the incidence of these tumors has increased more rapidly than that of bladder cancer and with a much lower male/female ratio, thus indicating that etiologies may differ for these urothelium-derived tumors (data not shown).

The present study is one of 2 case-control studies initiated in eastern Denmark in 1979 to evaluate reasons for the high risk of urinary tract tumors in Denmark. Results of the bladder cancer study have been reported previously (Jensen *et al.*, 1983, 1986, 1987*a,b*). This report describes the role of tobacco smoking in cancer of the renal pelvis and ureter, and compares the risk to that observed for bladder cancer in the same area. In addition, the role of occupational exposures in this cancer is also explored.

MATERIAL AND METHODS

Cases

It is difficult to distinguish between truly benign and invasive tumors of the urinary tract (Mostofi *et al.*, 1981), and all tumors of the renal pelvis and ureter have therefore been grouped together under the term "cancer". Since tumors of the renal pelvis and ureter are epidemiologically quite similar and derived from the same type of epithelium, they have been combined in the present study.

Patients studied had incident cancer of the ureter and renal pelvis as their first urinary tract tumor, and were below the age of 80 years at diagnosis. Between 1979 and 1982, cases from 27 hospitals serving the population of Copenhagen and

the surrounding island of Sjælland were reported by telephone to the study section of the Danish Cancer Registry in addition to routine notification to the Registry.

Altogether, 97 patients were reported to the study and 96 (99.0%) of these were interviewed. Approximately 45% (2.3 million) of the Danish population (5.1 million) lives in the eastern parts of the country where the study was carried out. It is estimated that some 80% of all eligible incident cases of renal pelvis and ureter cancer were enrolled in the study. In 79% of the cases, the tumors were located in the renal pelvis, including calyces, which is consistent with national cancer statistics. Seventy percent of the patients had symptoms for less than 6 months prior to interview and 19% had metastatic spread at the time of diagnosis. The diagnosis was histologically verified in 90% of the cases; the remainder were diagnosed by combinations of X-ray, surgery, and urinary cytology. Some 98% of all classified tumors were of the transitional-cell type, and 57% of these were grades I to II (Bergquist *et al.*, 1965).

Controls

Since case ascertainment was restricted to hospitals in eastern Denmark, controls were also chosen from these institutions. Three controls were selected per case matched for hospital, sex, and age in 5-year age groups. Patients with urinary tract and smoking-related diseases, *i.e.*, cancer of the lung, buccal cavity, pharynx and esophagus, as well as patients with chronic bronchitis and cardiac or vascular atherosclerosis, were not eligible as controls. Altogether, 288 persons were approached and interviewed as controls.

Interview

By means of a detailed, structured questionnaire, information was elicited by trained interviewers on demographic variables and on known and suspected risk factors for lower urinary tract cancers. The interview included questions about tobacco smoking, beverage consumption, use of artificial sweeteners, use of analgesics, occupation and related exposures. Almost all (94%) cases and controls were interviewed at the hospital immediately after admission.

If a person had ever smoked regularly, *i.e.*, at least one cigarette, cigar, cigarillo (cheroot), or pipe daily for 3 months or longer, a detailed smoking history was obtained. For each type of tobacco this included information on ages at starting and stopping, highest amount smoked regularly for a year, inhalation, use of filter cigarettes, and brand name of cigarettes. Limited information was collected by means of the

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Abbreviations: RR = relative risk; CI = confidence interval.

TABLE I – SMOKING HABITS AMONG CONTROL SUBJECTS FROM HOSPITALS FOR DANISH CASE-CONTROL STUDY OF RENAL PELVIS AND URETER CANCER

Smoking habit	Male				Female			
	−64 years		65+ years		−64 years		65+ years	
	Number	%	Number	%	Number	%	Number	%
Never smoked	5	7.5	17	15.0	18	31.0	17	34.0
Pipe only	3	4.5	7	6.2	0	—	0	—
Cigar only	3	4.5	11	9.7	2	3.4	8	16.0
Cigarette only	18	26.9	23	20.4	29	50.0	21	42.0
Mixed, including cigarettes	34	50.7	52	46.0	9	15.5	4	8.0
Mixed, no cigarettes	4	6.0	3	2.7	0	—	0	—
Total	67	100.0	113	100.0	58	100.0	50	100.0

TABLE II – SMOKING HABITS AND RELATIVE RISK OF RENAL PELVIS AND URETER CANCER
IN DENMARK, 1978–82

Smoking habit	Cases	Controls	RR[1]	95% CI
Never smoked	8	57	1.0	(R)[2]
Pipe only	1	10	2.2	(0.1–97)
Cigar only	4	24	1.3	(0.3–6.1)
Cigarette only	32	91	2.6	(1.0–6.7)
Mixed, cigarettes	48	99	3.8	(1.3–11.5)
Mixed, no cigarettes	3	7	6.5	(0.4–21.2)

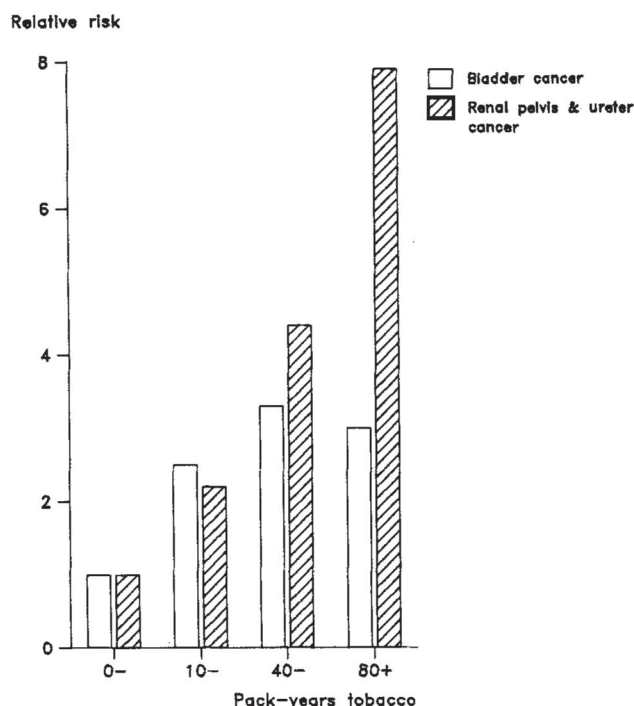[1]Adjusted for sex and age (−64 years, 65 + years).–[2](R) is the reference category.

FIGURE 1 – Dose-effect for lifetime tobacco consumption (pack-years) and risk of renal pelvis-ureter and bladder cancer in Danish men and women.

structured questionnaire on occupations and occupational exposures associated with lower urinary tract cancer in earlier investigations.

Analysis

Following examination of the separate association between pelvis-ureter cancer and daily amount and duration of smok-ing, tobacco consumption (cigarettes, pipe tobacco, cigars and cigarillos together) was calculated in pack-year equivalents, *i.e.*, 20 g of tobacco smoked per day for one year equals one pack-year. As in our previous analysis of bladder cancer risk (Jensen *et al.*, 1987*a*), a cigarette was counted as 1 g of tobacco, a cigar as 5 g, a cigarillo (or cheroot) as 3 g; pipe tobacco was measured directly as quantity (in g) consumed per week. The resulting continuous variable was categorized into 4 (males) or 3 (females) categories of lifetime tobacco consumption. For comparison, the smoking data from our parallel bladder cancer study (Jensen *et al.*, 1987*a*) were reanalyzed in an identical fashion.

The association between a potential risk factor and renal pelvis and ureter cancer was measured by the odds ratio as an estimate of the relative risk. The effects of potentially confounding variables including age (−64 year, 65+ year), sex and lifetime tobacco smoking were evaluated by stratified contingency table analysis. When no heterogeneity was observed, the influence of confounding factors was controlled in this way, summary RR were calculated by the maximum like-lihood method and 95% confidence intervals (CI) were obtained by the method of Gart (1970). Cases and controls with missing values for a particular variable were excluded from that computation. Whenever the limits of the CI do not include 1.0, the RR is considered to differ significantly from unity. Linear trend was measured by Mantel's extension of the Mantel-Haenszel procedure (Mantel, 1963).

RESULTS

Smoking habits

As in previous studies of smoking in relation to urinary tract cancer in Denmark, the present study shows a large diversity of smoking habits (Table I). Some 85% and 65% of the male and female controls, respectively, reported having smoked regularly. Some 70% of all men had regularly smoked ciga-rettes, but two-thirds of these had also regularly smoked pipes, cigars or cigarillos. Among women, 50–60% had smoked cigarettes, and the majority were exclusively cigarette smok-

TABLE III – LIFETIME TOBACCO CONSUMPTION AND RELATIVE RISK OF RENAL PELVIS AND URETER CANCER IN DENMARK, 1979–82

Lifetime tobacco consumption (pack-years)[1]	Male				Female				Male and female	
	Case	Control	RR[2]	95% CI	Case	Control	RR[2]	95% CI	RR[3]	95% CI
0–9	3	33	1.0	(R)[4]	8	48	1.0	(R)[2]	1.0	(R)[2]
10–39	13	63	2.2	(0.6–8.2)	16	42	2.2	(0.9–5.8)	2.2	(0.97–5.2)
40–79	25	55	5.0	(1.5–16.6)	12	18	4.0	(1.4–11.1)	4.4	(1.9–10.7)
80+	19	29	7.9	(1.9–39.1)	—	—	—	—	7.9	(1.9–39.1)
Trend test	—	—	—	$p < 0.001$	—	—	—	$p = 0.004$	—	$p < 0.001$

[1]Cigarette or pack-year equivalents for all types of tobacco (see text).–[2]Adjusted for age.–[3]Adjusted for age and sex.–[4](R) is the reference group.

TABLE IV – INFLUENCE OF CIGARETTE SMOKE INHALATION, CIGARETTE SMOKING CESSATION AND FILTER CIGARETTE SMOKING ON THE RISK OF RENAL PELVIS AND URETER CANCER IN DENMARK, 1979-82

Cigarette smoking habit	Cases	Controls	RR[1]	95% CI
Inhale, never/slightly	27	178	1.0	(R)[2]
Inhale, deeply	67	109	3.4	(1.9-6.1)
Current smoker	60	116	1.0	(R)[2]
Ex-smoker	20	74	0.6	(0.3-1.1)
Plain cigarettes	56	105	1.0	(R)[2]
Filtered cigarettes	23	82	0.5	(0.3-0.9)

[1]Adjusted for sex and lifetime tobacco consumption.–[2](R) is the referent group

TABLE V – OCCUPATIONS AND OCCUPATIONAL EXPOSURES AND RELATIVE RISKS OF RENAL PELVIS AND URETER CANCER IN DENMARK, 1979-82

Occupation/exposure	Sex	Exposed		RR[1]	95% CI
		Cases	Controls		
Chemical, petrochemical, plastics industries; gasoline, petroleum	M+F	14	14	4.0	(1.6-9.8)
Coke, coal	M	8	7	4.0	(1.2-13.6)
Asphalt, tar	M	9	6	5.5	(1.6-19.6)
Gasworks, installation	M	2	3	2.7	(0.3-23.4)
Dye-stuffs industry, dyeing	M+F	6	9	2.1	(0.6-7.0)
Rubber industry	M+F	4	7	1.6	(0.4-6.7)
Leather, tanning	M+F	7	11	2.2	(0.7-6.7)
Painter, paint manufacture	M+F	10	19	1.8	(0.7-4.6)
Iron/metal industry, blacksmith	M	17	41	1.4	(0.7-2.9)
Wood industry, woodwork	M	4	14	0.8	(0.2-2.7)
Textile industry	M+F	8	27	0.9	(0.4-2.4)
Hair-dressing	F	2	2	3.0	(0.3-33.0)
Cook, kitchen aid	M+F	7	25	0.7	(0.2-1.8)
Health care sector	M+F	4	24	0.4	(0.1-1.4)
Office work	M+F	19	61	1.0	(0.5-1.9)

[1]Relative to persons not in industry/not exposed. Adjusted for sex (when both sexes included) and lifetime tobacco consumption.

ers. Table I shows a tendency for more cigarette smokers among men and women below the age of 65 years compared to persons aged 65 years or more.

In Table II, the relative risks for different smoking habits are presented. Significantly increased RR are seen for exclusive smokers of cigarettes and for mixed smokers who had also smoked cigarettes regularly. For other smoking habits, numbers are too small to yield stable risk-estimates.

In view of the diversity of smoking habits (Table I) and the limited size of the study, all types of smoking were combined into lifetime tobacco use. Table III shows a highly significant trend in relative risk for both men ($p < 0.001$) and women ($p = 0.004$) with amount of tobacco consumed over a lifetime.

Men with a lifetime tobacco consumption of 80 or more pack-years have an almost 8-fold increase in risk compared to men with a consumption of less than 10 pack-years. For corresponding levels of consumption, the relative risks for men and women were quite similar.

Table IV shows the RR associated with various patterns of cigarette smoking. Persons who reported inhaling cigarette smoke deeply were at a significantly increased risk (RR=3.4) compared with persons who inhaled slightly, or not at all. Ex-smokers of cigarettes had a decreased risk (RR=0.6), although this decrease was not statistically significant (95% CI: 0.3–1.1) compared with current smokers of cigarettes, taking into account lifetime tobacco consumption; the data were in-

sufficient to enable risks to be estimated in relation to time since quitting, but there was an indication of a drop in risk soon after smoking cessation. Filter cigarette smokers had a significantly lower relative risk (RR=0.5) than smokers of plain cigarettes.

From 1979 to 1982, cases of bladder cancer (including papilloma) and randomly sampled controls from the population were investigated in greater Copenhagen, which covers 75% of the population included in the present study. The same questionnaire was employed in the 2 investigations and the smoking habits, as categorized in Table I, did not differ for the 2 control groups. The relative risks associated with ever having smoked different types of tobacco products were similar for the bladder cancer study and for the present investigation. A comparison of patients with pelvis-ureter and bladder tumors showed that the dose-effect was greater for renal pelvis-ureter tumors than for bladder cancer (Fig. 1) (trend test: $p=0.003$, one-sided).

Occupational exposures

Table V shows the relative risks associated with occupations and occupational exposures previously thought to be related to lower urinary tract cancer. The relative risks are adjusted for tobacco and sex. Because of the explorative nature of the study with regard to occupational exposures, the risk in each exposure category is compared with risk for persons not in that occupation, irrespective of possible exposure in other occupations. A significantly higher relative risk is seen for persons who worked in the chemical, petrochemical, or plastics industries, or who had been exposed to gasoline or petroleum products. Use of chemicals carries an RR of 5.0 (95% CI; 1.8–13.9) and exposure to vapors an RR of 5.6 (95% CI; 1.9–16.5). Similarly increased risks are seen for exposures to coal/coke and asphalt/tar. Employment at gas works or with gas installations, as well as exposures in a number of industries, including the iron/metal industry and painting, also carries increased risks, although none is significant.

DISCUSSION

The present investigation corroborates the role of smoking in the development of tumors of the renal pelvis and ureter, and the clear dose-effect of lifetime tobacco consumption (Table III) provides further evidence of the causal role of smoking in the etiology of these tumors. The effect is related to cigarette smoking, but detailed assessment of the risk in persons who smoked exclusively cigars or pipes is hampered by the limited number of observations. Compared with our parallel investigation of bladder cancer in the same population and time period (Jensen et al., 1987a), this study suggests that the relative risk associated with heavy smoking is 2.5 times greater for renal pelvis-ureter cancer than for bladder cancer (Fig. 1).

The results support similar findings from the United States, where Schmauz and Cole (1974), in a small study of 27 men with renal pelvis and ureter cancer, found a relative risk of 10 in smokers of more than 2½ packs of cigarettes per day and where McLaughlin et al. (1983) reported a significantly increased risk among both male and female cigarette smokers, with RRs of 11 among heavy smokers (more than 57 pack/years) compared with persons who never smoked. In England, Armstrong et al. (1976) noted a significant dose-effect in males with renal pelvis cancer. In Australia, McCredie et al. (1982, 1983a,b) found increased risks for cancer of the ureter and renal pelvis in both men and women who smoked tobacco (all types); men with a lifetime consumption of 250 kg or more of tobacco (corresponding to 35 pack-years or more) had a 4- to 5-fold increased risk, and a 5-fold increased risk for renal pelvis cancer was seen among women who had consumed 200

kg or more of tobacco (corresponding to 27 pack-years or more). Also, the study by McCredie et al. (1983b) indicated a steeper dose-response relationship for renal pelvis than for bladder cancer. When comparing the dose-response results of the present study with those previously reported, it must be kept in mind that the reference group in the current study includes light smokers (up to 10 pack-years) since the group of non-smokers was too small to yield stable risk estimates; among men, only one case reported that he had never smoked any type of tobacco.

Certain characteristics of cigarette smoking were investigated for the first time in our study of renal pelvis and ureter cancer. A clearly increased risk is associated with inhalation of cigarette smoke (Table IV) after accounting for the fact that heavy smokers inhale more deeply than light smokers. This finding is at variance with results reported from the large case-control study involving some 3,000 cases of bladder cancer in the United States (Hartge et al., 1987) and the bladder cancer study in Italy (Vineis et al., 1984). The apparently stronger associations of inhalation with renal pelvis and ureter cancer than with bladder cancer appear to be consistent with the greater risk associated with smoking. Studies from Italy have linked the risk of bladder cancer to the smoking of air-cured, black tobacco in particular (Vineis et al., 1984). Danish cigarettes contain a mixture of blond (Virginia) and black (Burley) tobaccos, and the relative amount of the latter has increased since the 1950s. Both our Danish bladder cancer study (Jensen et al., 1987a) and the present investigation indicate a role for pipe-smoking. Previous Danish studies of bladder cancer have also suggested that cigar smoking may increase the risk of that tumor (Lockwood, 1961; Mommsen and Aagaard, 1983) although this was not confirmed by our study in Copenhagen.

The present study also indicates a decreased risk among ex-smokers (RR=0.6) compared with current smokers. Although this is similar to previous observations for cancer of the bladder (Jensen et al., 1987a; Hartge et al., 1987; Vineis et al., 1984), it is more pronounced than the lowered risk reported by McLaughlin et al. (1983). The relative risk for smokers of filter cigarettes is about 50% of that for smokers of plain cigarettes (Table IV).

Several occupational exposures have been causally linked to bladder cancer (Matanoski and Elliott, 1981). The present case-control study indicates clearly increased risks of renal pelvis and ureter cancer for occupational exposures to coke, coal, asphalt, and tar products (Table V), possibly as a result of increased exposure to poly-aromatic hydrocarbons. This may also explain the increased risk among gas workers and installers and the association with exposure to gasoline and petroleum products. The approximately 2-fold higher risk for employment in the dye-stuffs, rubber, leather/tanning, painting and paint manufacturing industries suggests an etiological role for a variety of chemicals that need to be further specified in future occupational studies.

The occupational risk estimates in the present study are based on small numbers and chance cannot be excluded in all instances. Respondent bias seems to be limited, as indicated by the absence of increased risk for a number of industries. Previous studies of renal pelvis and ureter cancer also showed increased risks among persons exposed to coal, gas, tar, soot, and oils, and to a variety of chemicals (McLaughlin et al., 1983), and among leather workers (Schmauz and Cole, 1974; McLaughlin et al., 1983).

Our present investigation points unequivocally to tobacco smoking as the most important risk factor for renal pelvis and ureter cancer in Denmark. Up to 56% and 40% of all renal pelvis and ureter cancer in Danish men and women, respectively, would be avoided by stopping smoking. The indication of a steeper increase in relative risk for these sites than for the

bladder, and the correlation with inhalation, are consistent with a more pronounced carcinogenic effect of tobacco smoke on the proximal urothelium than on the distal parts. This could be due to the action of such agents on an epithelium at lower baseline risk, or to a degradation of tobacco carcinogens taking place in the urinary bladder. In view of these findings, the reasons for the much lower incidence of renal pelvis tumors compared with bladder tumors need explanation.

Irrespective of the possible mechanism involved, the majority of tumors of the renal pelvis and ureter could be avoided by abstaining from smoking. Prevention would be maximized by combining smoking abstinence with measures to decrease workplace exposure.

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