Nephrol Dial Transplant (1999) 14: 2892–2897

Nephrology
Dialysis
Transplantation

Original Article

Urothelial cancer at different tumour sites: role of smoking and habitual intake of analgesics and laxatives. Results of the Berlin Urothelial Cancer Study

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Abstract

Background. In Germany about 20 000 new cases of urothelial cancer (UC) and about 7500 deaths from bladder cancer alone occur each year. Among the manifold risk factors, little research has been done on the role of smoking and the habitual intake of analgesics and laxatives—practices that are common in parts of the German population. The aim of this study is to define the proportion of risk derived from these preventable habits for the development of UC at its different sites.

Subjects and methods. A case-control study in the area of the former West Berlin was performed from 1990 to 1995 including all newly diagnosed incident cases of UC from the eight hospitals of the study area. Study subjects and population-based controls individually matched by age (± 2 years) and sex were evaluated by a standardized face-to-face interview about the lifelong exposure to cigarette smoking, analgesics, and laxatives. Adjusted risk analysis was carried out for the main exposure variables in relation to the different sites of UC in the bladder, ureter, and renal pelvis.

Results. Six hundred and forty-seven cases of UC (571 bladder, 25 ureter, and 51 renal pelvis) and an identical number of controls were included in the analysis (response rate in cases, 84.6%; in controls, 70.2%). Smoking increased the risk of bladder cancer (BC) by an odds ratio (OR) of 3.22 (95% confidence interval (CI) 2.29–4.52), that of ureter (URC) or renal pelvis cancer (RPC) together by OR 6.20 (95% CI 2.04–18.81), and that of RPC alone by OR 5.91 (95% CI 1.47–23.66). Ex-smoking was associated with an increased risk for BC (OR 1.55, 95% CI 1.10–2.19). Intake of more than 1 kg of phenacetin in analgesic mixtures was associated with an OR of 5.28 for RPC (intake of $\geqslant 1$ kg paracetamol, OR 3.27; $\geqslant 1$ kg pyrazolones, 1.12) and 0.75 for BC (not significant). Laxatives significantly increased the risk of BC (OR 2.14, 95% CI 1.26–3.63) and RPC/URC (OR 9.62, 95% CI 1.01–91.24) in both sexes.

Conclusion. Habitual risks from smoking and intake of laxatives significantly contribute to the development of UC, especially of the renal pelvis and ureter cancer. Intake of at least 1 kg of analgesic substances (anilides, pyrazolones) as calculated from this study base is associated with increased but not significant risks for RPC. These data underline that restrictive and educational measurements focusing on common habits would have a strong impact on preventing UC in Germany.

Key words: analgesics; case-control study; habitual risks; laxatives; smoking; urothelial cancer

Introduction

The German incidence rates of cancer of the bladder (BC), ureter cancer (URC), and renal pelvis cancer (RPC) are internationally in the highest range [1,2]. Despite the incomplete data base in Germany, it is estimated that at least 20 000 new cases of urothelial cancer (UC) are diagnosed and about 7500 deaths from this disease occur each year [3, Hamburg Cancer Registry, Cancer Incidences 1994 (personal communication)]. Several risk factors, mostly defined by case-control studies, contribute to this type of cancer, including a broad spectrum of occupational, environmental, and life-style-related risks [1,2]. In general, the incidence of BC is 4–6 times higher in men, while URC and RPC is only twice as frequent in the male compared to the female population [1–3, Hamburg Cancer Registry, Cancer Incidences 1994 (personal communication)].

Smoking is a well-established risk factor for UC accounting for a 2 to 5-fold risk increase [2]. The aetiological role of chronic analgesic use—mostly

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intake of mixed compounds—in the development of UC decades ago is suspected from clinical observations obtained in Scandinavia and Switzerland [4,5]. In the nineties, however, a controversy has arisen about the causative role of analgesic substances, especially phenacetin and paracetamol, based on the results of different epidemiological studies [6–10]. In summary, anilides are supposed to increase the risk for BC 2 to 6-fold, in particular in females, and for URC and RPC 3 to 12-fold [1,2] but the results of these studies are limited by the small number of exposed subjects. The role of laxatives has never been evaluated in UC studies but their potential carcinogenic effects have been investigated in experimental settings [11–13]. First hints of the impact of habitual laxative intake in clinical settings stem from the early days of analgesic nephropathy [14], and the discussion has recently been stimulated by reports on carcinogenic effects of medicinal plants used in slimming substances [15].

The aim of this case-control study is to investigate potential preventable habitual risks for UC, namely smoking and chronic intake of analgesics and laxatives, practices that are popular in parts of the German population. These risk variables are assessed separately for UC at the different tumour sites because the clinical consequences of tumour location with regard to the loss of renal mass are very different for bladder cancer and ureter or renal pelvis tumours.

Subjects and methods

A case-control design was developed including patients with incidental UC as cases and population-based controls from the same study area. The following assumptions were made for sample size calculations: (i) minimum relative odds to be detected, 2.5; (ii) type I error (one-sided), 0.05; (iii) type II error, 0.10; and (iv) prevalence of regular drug intake (phenacetin, paracetamol) in controls, 3%. On this basis, a required minimal sample size of 463 was calculated with matching of one control to one case.

Selection of study subjects

Between October 1990 and June 1994, all patients with incidental UC (BC, ICD-9, 188; URC, ICD-9, 189.2; RPC, ICD-9, 189.1) diagnosed at one of the eight urology departments in the study area of the former West Berlin (for names and participants see Acknowledgements) were included. Diagnoses of UC were confirmed by biopsy in 98% of the cases, in 2% with advanced tumour stage by imaging techniques. Histological evaluation was performed by experienced pathologists at the local study centres.

Controls were selected from a master sample of the West Berlin population based on the roles of the central inhabitant registry. Subjects selected were individually matched by gender and age (± 2 years).

Only subjects of German nationality who had been living in Germany for at least 20 years were included. The following conditions led to exclusion of study subjects (cases/controls): (i) inability to follow the interview due to physical or mental incapacity (53/164); (ii) death (0/139); (iii) no longer living in the study area (0/100); (iv) less than 20 years living in Germany (12/16); (v) other tumours (9/0).

Interviews

Only study subjects having given informed consent were interviewed. Trained interviewers from non-medical professions evaluated lifelong drug intake, smoking history, different aspects of occupational and medical history, and lifestyle-related risks (only parts of these data included). For this purpose, a standardized questionnaire including several lists of analgesics and other drugs and a detailed smoking history which covered duration, frequency, intensity, and kind of exposure was prepared based on a standardized questionnaire used in a previous study [16].

Interviews in cases were obtained in the hospital at the time of diagnosis before discharge. In controls the interviews were performed in a private setting at home or at any place convenient for the individual subject. Controls were offered a small gratuity to stimulate attendance to the study.

Definition of risk variables

Smoking analysis was restricted to cigarette smoking. Reference group (never or rare smoking) included the category 'rare smoking' for subjects who had never smoked daily. Pipe or cigarillo smoking was rare in the study subjects and not included in this analysis. Risk calculations for smoking were truncated to the time period of 2 years before tumour manifestation. Subjects who have stopped smoking at least 2 years before interview were defined as ex-smokers.

Classification of socioeconomic status (SES) is based on the level of school and professional education. The score ranges from 'low' (neither school nor professional graduation) over 'middle' and 'high' to 'very high' (university graduation, reference group).

The analgesic intake was analysed for lifelong cumulative amount of <1 kg and for $\geqslant 1$ kg. Rare intake was classified as intake of less than one analgesic dose per month. Undefined intake was classified for subjects with unclear intake data only.

The analysis of the intake of laxatives based on contact laxatives only (anthranoides and chemicals) and was categorized by duration of intake (<1 year, $\geqslant 1$ year). Habitual use was considered in subjects with a daily intake of any laxative substance lifelong for more than 1 year.

Because of the small number of incident ureter cancers, this tumour site was analysed together with renal pelvis tumours.

Data analysis

Data analysis used standard methods of case-control analysis [17–19]. The analysis was performed by conditional logistic regression with SAS procedure PHREG. The assessment of analgesic and laxative risks was adjusted (i) for smoking, ex-smoking, socioeconomic status, and (ii) for smoking, ex-smoking, socioeconomic status, and laxatives respectively phenacetin intake ($\geqslant 1$ kg).

Results

During the study period, a total of 840 cases with suspected UC and 1340 population-based controls were included in the initial study base. From these, 74 cases and 419 controls had to be excluded. The main cause of exclusion in cases was severely impaired physical

and mental condition resulting in the incapacity to follow the interview ($n=53$). In controls, incapacity to respond to the interview yielded 164 subjects, 139 died before the time of the interview, and 100 moved out of the study area. Thus, 84.6% of cases and 70.2% of controls underwent the interview and were individually matched for analysis (Table 1). The mean age of study subjects was 70.4 years; 80% of all subjects were in the age group of 60–89 years and 2% in the age group of 90 years and above. Age was identical in 94.3% of the matched pairs, in 1.4% the difference in age was 2 years.

In the case group the proportion of BC reached 88.3%; 3.9% of the subjects had URC and 7.9% RPC (Table 2). While UC of the bladder and ureter showed an almost equal distribution between both sexes, RPC was almost twice as frequent in females.

Smoking was highly prevalent in cases (45.4%) and in controls (24.6%) while ex-smoking was almost equally distributed in both groups (30.1% in cases, 36.6% in control subjects). Smoking significantly increased the risk of UC at all cancer sites: 3.22 OR for BC, 5.91 OR for RPC, and 6.20 OR for the combined analysis of URC or RPC. Ex-smokers had a moderately increased risk for BC (1.55 OR) but not for URC or RPC (Table 3). For bladder cancer and RBC, highest risks was found for lower socioeconomic status while for renal pelvis or ureter cancer highest risk ratio were calculated for subjects with high SES.

Exposure to mixed compounds of analgesics (at least 1 kg of analgesic substances lifelong) showed a substance-specific association with markedly increased risk ratios for RPC, moderately for RPC/URC, and no increased risk ratios for BC. Among the different analgesic substances anilides (intake >1 kg) were associated with the highest risks for RPC (phenacetin OR 5.28, paracetamol OR 3.27). Intake of pyrazolones showed a small increase of risks for RPC (OR 1.12). None of the risk ratios reached statistical significance (Table 4). Adjustments for laxative intake decrease the risks of anilides for RPC and increase slightly risks for RBC/URC. The analysis of mixed-compound intake less <1 kg of analgesic substances lifelong and mono-analgesic intake revealed no rise of the risk ratios for any UC tumour sites.

Laxatives (anthranoides and chemical laxatives) were taken by 9.7% of the cases and 4.5% of the control subjects with equal proportions in both genders (Table 5). The intake of laxatives for at least 1 year increased the overall risk for UC to an OR of 2.65, for BC to an OR of 2.14, and excessively for RPC/URC to an OR of 9.62 (Table 5). Intake for less than 1 year showed no sign of enhancing the risk of UC.

Adjustment for an intake of 1 kg phenacetin and more did not alter the risks of laxative intake.

Table 1. Study group and response

	Cases *n* (%)	Controls *n* (%)
Total study population	840	1340
Exclusion[1]	74	419
Study group	766 (100)	921 (100)
Subjects unavailable	34 (4.4)	1 (0.1)
Refusals	82 (10.7)	271 (29.4)
Interviews not completed	2 (0.3)	2 (0.2)
Interview responses	648 (84.6)	647 (70.2)
Unmatched	1	0
Individual matched pairs	647 (100)	647 (100)
Men	415 (64.1)	415 (64.1)
Women	232 (35.9)	232 (35.9)

[1]For definition, see subjects and methods.

Table 2. Distribution of urothelial cancer at different sites in the study group

	Total *n* (%)	Men *n* (%)	Women *n* (%)
Renal pelvis	51 (7.9)	23 (5.5)	28 (12.1)
Ureter	25 (3.9)	14 (3.4)	11 (4.7)
Bladder	571 (88.3)	378 (91.1)	193 (83.2)
Total	647 (100)	415 (100)	232 (100)

Discussion

In this case-control study smoking and—for the first time—laxative intake were identified to increase the risk of urothelial cancer significantly, especially that of the renal pelvis and the ureter, while chronic intake of mixed-compound analgesics, which traditionally contained anilides and pyrazolones, revealed increased, but not statistically significant, odds for renal pelvis and only small effects for ureter cancer.

The association of smoking and bladder cancer has been established in more than 30 case-control studies and in 10 cohort studies [reviewed in 2]. Overall, smokers appear to have two to three times the risk of non-smokers, which is consistent with the 3.2-fold risk found in this study. Cessation of smoking decreases the risk of BC in time but the risk excess persists in 30–60% of subjects even more than 10 years after quitting [2]. In the present study ex-smokers had a risk excess of over 50%. Epidemiological studies of RPC and URC have demonstrated 2.5–7 times higher risks for smokers, with increasing risks for heavy smoking [reviewed in 1]. Consistent with these data, our study shows the risk of renal pelvis or ureter cancer to be six times higher for regular smokers than for non-smokers or rare smokers.

Previous studies have linked heavy use of analgesics, especially preparations containing phenacetin, to cancer of the bladder [reviewed in 2] and of the renal pelvis or ureter [reviewed in 1]. McCredie and co-workers [6,20] found a relative risk of 2.0 in Australian women who had a lifetime consumption of at least 1 kg. Piper and co-workers [7] reported a relative risk of 6.5 in US women aged 20–44 years who had used phenacetin-containing compounds for at least 30 days per year. Assessment of paracetamol

Table 3. Smoking, socioeconomic status (SES) and the risk of urothelial cancer at different tumour sites

	Renal pelvis *n* (%) cases/controls OR (95% Cl)[1]	Renal pelvis or Ureter *n* (%) cases/controls OR (95% Cl)[1]	Bladder *n* (%) cases/controls OR (95% Cl)[1]
Smoking			
Never/rare[2] (reference group)	14 (27.5)/21 (41.2) 1.00	20 (26.3)/33 (43.4) 1.00	138 (24.2)/218 (38.2) 1.00
Ex-smokers	9 (17.6)/17 (33.3) 0.97 (0.27–3.45)	15 (19.7)/28 (36.8) 1.00 (0.31–3.21)	180 (31.5)/209 (36.6) 1.55 (1.10–2.19)
Current smokers	28 (54.9)/13 (25.5) 5.91 (1.47–23.66)	41 (53.9)/15 (19.7) 6.20 (2.04–18.81)	253 (44.3)/144 (25.2) 3.22 (2.29–4.52)
SES			
Very high SES (reference group)	5 (9.8)/13 (25.5) 1.00	6 (7.9)/15 (19.7) 1.00	71 (12.4)/102 (17.9) 1.00
High SES	11 (21.6)/9 (17.6) 2.61 (0.70–9.68)	15 (19.7)/10 (13.2) 3.14 (0.95–10.30)	92 (16.1)/114 (20.0) 1.16 (0.76–1.76)
Middle SES	26 (51.0)/23 (45.1) 2.40 (0.80–7.26)	42 (55.3)/37 (48.7) 2.48 (0.91–6.79)	277 (48.5)/252 (44.1) 1.56 (1.10–2.20)
Low SES	9 (17.6)/6 (11.8) 3.19 (0.74–13.75)	13 (17.1)/14 (18.4) 1.97 (0.59–6.57)	131 (22.9)/103 (18.0) 1.86 (1.22–2.83)

[1]Odds ratio (95% confidence interval); [2]For definition see subjects and methods.

Table 4. Analgesic intake and the risk of urothelial cancer at different tumour sites

	Renal pelvis *n* (%) cases/controls OR adj. (95% Cl)	Renal pelvis or ureter *n* (%) cases/controls OR adj. (95% Cl)	Bladder *n* (%) cases/controls OR adj (95% Cl)
No/rare intake § (reference group)	20 (39.2)/19 (37.3) 1.00	31 (40.8)/31 (40.8) 1.00	286 (50.1)/269 (47.1) 1.00
Only other intake $/undefined intake §	4 (7.8)/4 (7.8)	6 (7.9)/5 (6.6)	23 (4.0)/27 (4.7)
	0.90 (0.15–5.31) 0.79 (0.13–4.98)*	0.95 (0.20–4.60) 1.14 (0.21–6.24)*	0.87 (0.47–1.58) 0.92 (0.50–1.69)*
All analgesics[1]:			
Intake <1 kg	9 (17.6)/14 (27.5) 0.34 (0.06–1.98) 0.22 (0.03–1.59)*	17 (22.4)/20 (26.3) 0.67 (0.19–2.34) 0.53 (0.14–1.99)*	135 (23.6)/167 (29.2) 0.83 (0.61–1.13) 0.85 (0.62–1.16)*
Intake ⩾1 kg	18 (35.3)/14 (27.5) 0.84 (0.22–3.18) 0.40 (0.07–2.18)*	22 (28.9)/20 (26.3) 0.64 (0.21–1.99) 0.44 (0.12–1.58)*	127 (22.2)/108 (18.9) 1.04 (0.74–1.47) 1.05 (0.75–1.47)*
Mixed compounds only (⩾ 1 kg)	16 (31.4)/9 (17.6) 1.35 (0.32–5.72) 0.87 (0.17–4.58)*	19 (25.0)/14 (18.4) 0.90 (0.28–2.87) 0.68 (0.19–2.42)*	87 (15.2)/76 (13.3) 1.0 (0.67–1.49) 1.02 (0.68–1.52)*
Substance specific risks: (Intake ⩾1 kg)			
Phenacetin	7 (13.7)/2 (3.9) 7.32 (0.56–96.07) 5.28 (0.34–81.03)*	7 (9.2)/3 (3.9) 1.76 (0.27–11.23) 1.78 (0.24–13.25)*	23 (4.0)/23 (4.0) 0.72 (0.38–1.38) 0.75 (0.39–1.43)*
Paracetamol	6 (11.8)/2 (3.9) 4.76 (0.38–59.37) 3.27 (0.25–43.02)*	6 (7.9)/3 (3.9) 1.64 (0.21–12.49) 2.25 (0.28–17.96)*	11 (1.9)/13 (2.3) 0.77 (0.31–1.90) 0.83 (0.33–2.07)*
Acetylsalicylic acid	13 (25.5)/9 (17.6) 0.94 (0.23–3.93) 0.55 (0.11–2.77)*	15 (19.7)/12 (15.8) 0.79 (0.23–2.75) 0.61 (0.16–2.24)*	72 (12.6/57 (10.0) 1.07 (0.72–1.61) 1.09 (0.73–1.64)*
Pyrazolones[2]	9 (17.6)/4 (7.8) 1.82 (0.29–11.55) 1.12 (0.15–8.31)*	11 (14.5)/4 (5.3) 1.38 (0.28–6.87) 1.04 (0.18–5.84)*	43 (7.5)/44 (7.7) 0.83 (0.49–1.38) 0.84 (0.50–1.40)*

Odds ratio (95% confidence interval) adjusted for smoking, ex-smoking, socioeconomic status.
*adjusted for smoking, ex-smoking, socioeconomic status, laxative intake.
§For definition see subjects and methods.
$Only other analgesics: other than anilides, salicylates, pyrazolones.
[1]Single and mixed compounds of anilides, salicylates, pyrazolones.
[2]Pyrazolones: Metamizole sodium, phenazone, aminophenazone, propyphenazone.

Table 5. Laxative intake and the risk of urothelial cancer

	n (%) cases/controls	OR adj. (95% confidence interval)#	
No intake (reference group)	584 (90.3)/618 (95.5)	1.00	
Intake	63 (9.7)/29 (4.5)	2.52 (1.52–4.18)	2.52 (1.52–4.17)*
Intake by gender:			
Men	28 (4.3)/14 (2.2)	2.67 (1.26–5.66)	2.67 (1.26–5.66)*
Women	35 (5.4)/15 (2.3)	2.46 (1.23–4.93)	2.47 (1.23–4.94)*
Intake by tumour site:			
Bladder	50 (7.7)/27 (4.2)	2.14 (1.26–3.63)	2.14 (1.26–3.63)*
Renal pelvis or ureter	13 (2.0)/02 (0.3)	9.34 (1.05–83.25)	9.62 (1.01–91.24)*
Intake by duration:			
<1 year	03 (0.5)/03 (0.5)	1.31 (0.22–7.78)	1.32 (0.22–7.86)*
$\geqslant 1$ year	60 (9.3)/26 (4.0)	2.64 (1.57–4.46)	2.65 (1.57–4.47)*

#Odds ratio adjusted for smoking, ex-smoking and socioeconomic status.
*Adjusted for smoking, ex-smoking, socioeconomic status and phenacetin intake ($\geqslant 1$ kg).

(acetaminophen) in these studies revealed no risk increase for BC even after heavy use [6,7].

In RPC and URC phenacetin has been established as a risk factor (3–12-fold risk increase [1]). In contrast to its role in BC, paracetamol has been suggested as a risk for cancer of the renal pelvis [9,20,25] and ureter [20]. The present study found phenacetin and paracetamol to be associated with a 3–5-fold risk for renal pelvis and only slightly increased risk for the combined analysis of RPC or URC. Similar to previous studies, the number of exposed subjects was small but the risk excess shows identical levels. Phenacetin was banned in 1986 from the West German pharmaceutical market. So far, we cannot separate the effect of previous phenacetin intake and subsequent use of paracetamol in heavy analgesic users. In view of these findings and data from the literature [9,20] we believe that the measure of replacing phenacetin by paracetamol in the eighties may not result in lowering the burden of cancer due to heavy intake of analgesic compounds. The role of pyrazolones, which showed a small risk increase for RPC in this study, has never been investigated in urothelial cancer studies.

The lack of significance in the risk relation between analgesics and UC in our study was clearly related to two facts. First, the proportion of heavy analgesic use was unexpectedly high in controls (intake of at least 1 kg of analgesics lifelong 20%; mixed compounds 14%); secondly, the number of cases with renal pelvis cancer, which had the highest risks, was small. Both cause a type II error and do not exclude hazards of analgesics concerning urothelial cancer.

The role of laxatives in the development of urothelial cancer has never been evaluated in human studies. In our study exposure to anthranoids and chemical laxatives shows a significant hazardous association with duration of intake for at least 1 year, is related to both sexes, doubles the risk of bladder cancer, and is associated with a 9-fold risk for RPC or URC. Although the latter finding is based on small numbers, it is in accordance with data on the carcinogenic potential reported in the literature [11–13,22–24] and suggests that chronic (habitual) intake of specific laxatives significantly contributes to the development of UC.

Experimental evidence for the multiple carcinogenic effects of laxatives, especially at the renal and urinary tract site, was obtained in long-term animal studies [12]. With regard to the urinary tract, in women the risk of laxative intake for the development of calculi formation has been emphasized [21], and dietary supplementation studies with bisacodyl-fed rats have proved a relationship between stone formation and urothelial proliferative lesions [22].

In summary, smoking and the habitual intake of analgesics, in particular of anilide-containing mixtures, and of laxatives seem to contribute significantly to the development of UC at the different tumour sites. These drugs, as well as other herbal cocktails recently suggested by Belgian pharmacists [15], are not free of hazards and should not be taken habitually. Due to the results of epidemiological studies in 1986 [16], German government authorities enforced the replacement of phenacetin by paracetamol (acetaminophen) and limited the package size of these OTC analgesics. However, the sale of compound analgesics has remained almost unchanged. Recently, the package size of OTC anthranoid laxatives has been restricted, together with a recommendation to limit intake to 2 weeks. We do not believe that these measures will effectively reduce the potential harm of these drugs. Further studies are strongly warranted. Health authorities are urged strictly to regulate the use of those OTC drugs that are harmful when taken habitually. The results of our study again underline the need for doctors and health-care advisors to educate people to refrain from popular habits such as smoking, analgesic use, and chronic laxative intake.

Acknowledgements. Berlin Urothelial Cancer Study (BUS) is supported by grant No. Fo 2.1–68502–125 of the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) (Germany). We acknowledge the participation of the following urological departments which contributed their patients to the study: University Hospital Rudolf-Virchow (Prof. Nagel, Dr Wulsten), Neukölln Hospital (Prof. Schabert), Moabit Hospital (Dr Heinrich, Prof.

Fabricius), Urban Hospital (Prof. Weißbach), Auguste Victoria Hospital (Prof. Kuntz), Franziskus Hospital (Prof. Kollwitz, Prof. Beer), Humboldt Hospital (Dr Hasselmann).

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Received for publication: 14.10.98
Accepted in revised form: 14.7.99