

POSSIBLE RELATION BETWEEN HYPERTENSION AND CANCERS OF THE RENAL PELVIS AND URETER

Kai-Li LIAW^{1*}, Martha S. LINET¹, Joseph K. McLAUGHLIN², Mimi C. YU³, Janet B. SCHOENBERG⁴, Charles F. LYNCH⁵, Shelley NIWA⁶, and Joseph F. FRAUMENI, Jr.¹

¹Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD

²International Epidemiology Institute, Rockville, MD

³Department of Preventive Medicine, School of Medicine, University of Southern California, Los Angeles, CA

⁴New Jersey Department of Health, Trenton, NJ

⁵Department of Preventive Medicine and Environmental Health, College of Medicine, University of Iowa, Iowa City, IO

⁶Westat Inc., Rockville, MD

To evaluate the relationship of selected medical conditions and medications with cancers of the renal pelvis and ureter, we interviewed 308 subjects with renal pelvis cancer, 194 subjects with ureter cancer and 496 control subjects in 3 areas of the United States. After controlling for the effects of smoking, age, gender and geographic residence, a history of hypertension (reported to have been diagnosed more than 5 years before interview) was associated with a small but significantly increased risk (odds ratio [OR] = 1.3; 95% confidence interval [CI], 1.0–1.8), whereas no relationship was observed with a variety of other medical conditions or medications. Stratified analysis showed that the risk associated with hypertension was twice as high among users of diuretics or other antihypertensive drugs (OR = 2.4; 95% CI, 1.1–4.9) as it was among those who never used these medications (OR = 1.2; 95% CI, 0.8–1.7). Our findings suggest that the association previously reported between hypertension and renal cell cancer may extend to cancers of the renal pelvis and ureter. *Int. J. Cancer*, 70: 265–268, 1997.

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Cancers of the renal pelvis and ureter, both lined by transitional epithelium, are uncommon tumors that account for less than 1% of all newly diagnosed cancers in the United States (Devesa *et al.*, 1990). However, the incidence rates have been rising by 2 to 4% annually among both men and women (Devesa *et al.*, 1990). Although there have been relatively few epidemiologic studies, the major risk factor is cigarette smoking, which is believed to account for most of these tumors (McLaughlin *et al.*, 1992).

Previous studies have linked heavy use of analgesics, especially preparations containing phenacetin, to an elevated risk of renal pelvis and ureter cancers (McCredie *et al.*, 1982, 1993; McLaughlin *et al.*, 1983; Jensen *et al.*, 1989). However, data from the present study revealed no association (Linnet *et al.*, 1995), probably because phenacetin was discontinued many years ago in the United States and the carcinogenic effects may no longer be apparent. To investigate further the role of prior medical conditions and pharmaceutical agents in the development of these cancers, we examined data from a large-scale, population-based, case-control study conducted in 3 geographic areas in the United States.

METHODS

Detailed methods for this study have already been described (McLaughlin *et al.*, 1992; Linnet *et al.*, 1995). Briefly, cases were individuals aged 20–79, newly diagnosed with microscopically confirmed cancers of the renal pelvis or ureter between January 1, 1983, and December 31, 1986, and living in New Jersey, Iowa or Los Angeles County, California. Non-white cases in these areas were excluded from the study because of very small numbers. Population-based control subjects were frequency-matched to the index cases based on age (5-year group), sex, and geographic area and were chosen by random digit dialing (RDD) (Waksberg, 1978) for cases younger than 65 or selected from Medicare files of the

Health Care Financing Administration (HCFA) for cases aged 65 or older. A structured questionnaire was administered in person by a specially trained interviewer to elicit detailed information on medical history (including urinary tract stones, infections, and diseases; diabetes; angina; heart attack; stroke; and hypertension) and use of specific medications, including 14 diuretics, 7 antihypertensives, 10 amphetamine-containing appetite suppressants and female hormones (estrogen and oral contraceptives). Because it is unlikely that the next-of-kin could provide accurate and detailed information on medical or medication history, deceased and very ill cases were excluded.

Data on preexisting medical conditions and medication use, including duration and age at diagnosis or first exposure, were treated as categorical variables. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated for each study variable, using multiple logistic regression models (Breslow and Day, 1980). Because smoking was previously reported as the major risk factor in this study (McLaughlin *et al.*, 1992), it was adjusted for in the regression models (never, <33, 33–53, and >53 pack-years) along with other known or likely confounders including age, gender, and geographic area of residence. The models did not include use of analgesics because no associated risks were found in our study.

RESULTS

A total of 502 cases and 496 controls completed the in-person interview, representing 58% of ascertained cases, 54% of the RDD controls, and 66% of the HCFA controls. Among cases, the major reasons for non-interviews were death or illness (25%) and physician or subject refusals (11%). For RDD controls, the response rate at the household screening phase was 92%, but 59% at the interview phase. The major reasons for non-response among RDD controls at the interview phase were refusals (23%) and untraceable respondents and language problems (13%). The major reasons for non-response among HCFA controls were refusals (16%), death or illness (7%), and untraceable respondents and language problems (8%). A comparison of age, sex, and cancer site distribution revealed that distribution of sex and cancer site was similar between interviewed and non-interviewed cases, although the non-interviewed were slightly older.

Of the 502 cases interviewed, 308 (193 males and 115 females) had renal pelvis cancer and 194 (138 males and 56 females) had ureter cancer. The histologic type was transitional cell in 97% and squamous cell or papillary in 3%. Among interviewed subjects,

*Correspondence to: National Cancer Institute, 6130 Executive Boulevard, EPN 443, Rockville, MD 20852, USA. Fax: (301) 402-0916. e-mail: LIAWK@EPNDCE.NCI.NIH.GOV

64% of cases and 66% of controls were male. Among cases, 78% were older than age 60 at interview; 76% of controls fell into the same age category. In addition, the education level was similar between cases and controls. The results are presented here for renal pelvis and ureter cancers combined because risk estimates associated with specific medical conditions and medications were similar by subsite. In addition, the results for men and women are combined because no significant gender differences were seen in the risk estimates.

The risks for cancers of the renal pelvis and ureter associated with various medical conditions are shown in Table I. To minimize possible misclassification between these conditions and early manifestations of the cancers, those conditions diagnosed within 5 years before interview were excluded from analysis. As expected, results without censoring the medical conditions and drug use reported within 5 years before interview showed a large increase in risks associated with kidney diseases, stones, injuries, and infections. However, when the most recent medical conditions and drug use were excluded from the analysis, the excess risks disappeared except for a non-significant 50% excess among those reporting a history of urinary tract infections. Risks were not increased among those who reported other urinary tract disorders, including benign renal tumors or cysts, hydronephrosis, or renal failure. Also, no association was found with other medical conditions including diabetes, angina, heart attack, and stroke. However, a small (30%) but significant increase in risk was associated with a history of hypertension. The level of excess risk remained about the same regardless of the interval between the first diagnosis of hypertension and the interview (data not shown).

TABLE I – ODDS RATIOS (OR) AND 95% CONFIDENCE INTERVALS (CI) FOR CANCERS OF THE RENAL PELVIS AND URETER ASSOCIATED WITH MEDICAL CONDITIONS FIRST DIAGNOSED MORE THAN 5 YEARS BEFORE INTERVIEW

Medical condition	Cases ¹ (%)	Controls ¹ (%)	OR ²	95% CI ²
Kidney stones				
No	425 (90.2)	451 (92.4)	1.0	—
Yes	46 (9.8)	37 (7.6)	1.2	0.8–2.0
Bladder stones				
No	489 (98.6)	484 (99.0)	1.0	—
Yes	7 (1.4)	5 (1.0)	1.2	0.4–4.2
Injury to the kidney				
No	488 (99.0)	491 (99.0)	1.0	—
Yes	5 (1.0)	5 (1.0)	0.8	0.2–3.0
Kidney infections				
No	416 (93.5)	464 (94.5)	1.0	—
Yes	29 (6.5)	27 (5.5)	1.3	0.7–2.3
Bladder infections				
No	400 (86.6)	402 (85.5)	1.0	—
Yes	62 (13.4)	71 (15.0)	0.9	0.6–1.4
Other urinary tract infection				
No	451 (94.9)	463 (96.1)	1.0	—
Yes	24 (5.1)	19 (3.9)	1.5	0.8–2.8
Diabetes				
No	451 (94.5)	446 (92.9)	1.0	—
Yes	26 (5.5)	34 (7.1)	0.6	0.4–1.1
Angina				
No	457 (94.0)	452 (95.2)	1.0	—
Yes	29 (6.0)	23 (4.8)	1.1	0.6–2.0
Heart attack				
No	438 (91.8)	446 (93.9)	1.0	—
Yes	39 (8.2)	29 (6.1)	1.3	0.8–2.2
Stroke				
No	478 (98.8)	472 (97.3)	1.0	—
Yes	6 (1.2)	13 (2.7)	0.4	0.2–1.2
Hypertension				
No	293 (66.9)	321 (72.1)	1.0	—
Yes	145 (33.1)	124 (27.9)	1.3	1.0–1.8

¹Subjects with missing values were excluded from the analysis.—

²Adjusted for age, sex, geographic site, smoking, and history of hypertension (including that diagnosed within 5 years of interview) when applicable.

As shown in Table II, there were slight and non-significant increases in risks associated with diuretic and other antihypertensive drugs used more than 5 years before interview, but these risks faded after adjustment for a history of hypertension. Risks were higher among individuals using diuretics for 5 or more years and among those aged 60 or older at first use, but the excesses were not significant. No patterns by duration or age at first use were seen for other antihypertensive drugs. No excess risk was seen among those who had taken both diuretics and other antihypertensive drugs. Further evaluation by type of diuretic (loop, thiazides, and potassium-sparing) or antihypertensive agent (beta-blockers vs. others) showed little difference between cases and controls (data not shown).

As expected, use of diuretics and antihypertensives was highly correlated with a history of hypertension among both cases and controls, but a somewhat higher fraction of cases than controls took these medications for elevated blood pressure (84% of diuretic users among cases and 70% among controls; 86% of antihypertensive drug users among cases and 77% among controls). To help disentangle the relationships among hypertension, drug therapy, and cancer risk, we evaluated history of hypertension stratified by ever vs. never use of diuretics and other antihypertensive drugs. The risk associated with hypertension was twice as high among users of diuretics or antihypertensive drugs (OR = 2.4; 95% CI, 1.1–4.9) as it was among non-users (OR = 1.2; 95% CI, 0.8–1.7).

There was no excess risk related to amphetamine-containing appetite suppressants or female hormones. This remained true when occasional vs. regular use, duration of regular use, and age at first regular use were taken into account (data not shown).

DISCUSSION

In the largest population-based, case-control study to date of cancers of the renal pelvis and ureter, a survey was made of preexisting medical conditions and medication use. A significant excess risk was associated with a history of hypertension, particularly among users of diuretics or other antihypertensive drugs. It is possible that these differences may simply reflect the severity of hypertension among medication users. However, this finding still merits further investigation, because a number of previous studies have linked hypertension to an excess risk of renal cell cancer but not of tumors of the renal pelvis and ureter. In contrast, we found no associations with other medical conditions or medications, including phenacetin-containing analgesics (Linnet *et al.*, 1995), which were previously linked to these tumors when use was common.

In evaluating the positive association with hypertension, we tried to sort out the possible effects of treatment on cancer risk. Consistent with earlier studies (McCredie and Stewart, 1992; Lindblad *et al.*, 1993), we found no significant increased risks associated with diuretic use. In contrast, use of diuretics has been suggested as a risk factor in several studies of renal cell cancer (Kreiger *et al.*, 1993; Mellemegaard *et al.*, 1992; McLaughlin *et al.*, 1995). Although the association is not established as causal, it is noteworthy that diuretics affect the renal tubules that represent the tissue of origin for renal cell cancer (de Leeuw *et al.*, 1994). However, the effects, if any, on the transitional cells of the renal pelvis and ureter are not clear.

Our study also revealed no excess risk of renal pelvis and ureter cancers among men and women taking other classes of antihypertensive drugs, including beta-blockers. This finding stands in contrast to an Australian case-control study reporting a significant 2-fold excess of renal pelvis cancer among women using non-diuretic antihypertensive drugs, especially beta-blockers (McCredie and Stewart, 1992). In addition, an excess of renal cancer has been suggested in 2 prospective surveys (Fletcher *et al.*, 1993; Hole *et al.*, 1993) of hypertensive patients taking beta-blockers, but the subsites were not specified and the relation was attributed to hypertension rather than medication use. Reasons for the differences are not clear, but the negative findings in our study may be

TABLE II – ODDS RATIOS (OR) AND 95% CONFIDENCE INTERVALS (CI) FOR CANCERS OF THE RENAL PELVIS AND URETER ASSOCIATED WITH USE OF DIURETICS AND ANTIHYPERTENSIVE DRUGS MORE THAN 5 YEARS BEFORE INTERVIEW

Drug use	Cases ¹ (%)	Controls ¹ (%)	OR ²	OR ³	95% CI ³
Diuretic drugs					
Ever use ⁴					
No	395 (78.8)	398 (80.2)	1.0	1.0	—
Yes	106 (21.2)	98 (19.8)	1.2	1.0	0.7–1.5
Years of regular use					
Never	401 (80.0)	409 (82.6)	1.0	1.0	—
<2	20 (4.0)	23 (4.6)	1.1	1.0	0.5–2.0
2–5	32 (6.4)	30 (6.1)	1.2	1.1	0.6–1.9
>5	48 (9.6)	33 (6.7)	1.6	1.4	0.8–2.3
Years of age at first regular use					
Never	401 (80.0)	409 (82.6)	1.0	1.0	—
<50	22 (4.4)	19 (3.8)	1.4	1.2	0.6–2.5
50–59	29 (5.8)	31 (6.3)	1.0	0.9	0.5–1.6
≥60	49 (9.8)	36 (7.3)	1.6	1.4	0.8–2.3
Other antihypertensive drugs					
Ever use ⁴					
No	427 (85.2)	428 (86.3)	1.0	1.0	—
Yes	74 (14.8)	68 (13.7)	1.1	0.9	0.6–1.4
Years of regular use					
Never	427 (85.9)	431 (86.9)	1.0	1.0	—
<2	13 (2.6)	14 (2.8)	0.8	0.7	0.3–1.6
2–5	29 (5.8)	26 (5.2)	1.3	1.1	0.6–2.0
>5	28 (5.6)	25 (5.0)	1.1	0.9	0.5–1.7
Years of age at first regular use					
Never	427 (85.9)	431 (86.9)	1.0	1.0	—
<50	17 (3.4)	9 (1.8)	2.0	1.7	0.7–4.0
50–59	29 (5.8)	31 (6.3)	1.0	0.8	0.4–1.5
≥60	24 (4.8)	25 (5.0)	0.9	0.8	0.5–1.5
Drug use alone and in combination⁴					
None	360 (71.9)	363 (73.2)	1.0	1.0	—
Diuretics only	67 (13.3)	65 (13.1)	1.1	1.0	0.6–1.5
Antihypertensives only	35 (7.0)	35 (7.1)	1.0	0.8	0.5–1.5
Both diuretics and antihypertensives	39 (7.8)	33 (6.6)	1.3	1.0	0.6–1.8

¹Subjects with missing values were excluded from the analysis.—²Adjusted for age, sex, geographic sites, and smoking.—³Adjusted for age, sex, geographic site, smoking, and history of hypertension (including that diagnosed within 5 years before interview).—⁴First started more than 5 years before interview.

related to the exclusion of medications used within 5 years of interview.

Since the use of diuretics, beta-blockers and other antihypertensive drugs is highly correlated with hypertension, it is difficult to differentiate the effects of hypertension and its treatment on cancer risk. When we stratified by ever vs. never use of either diuretics or other antihypertensives, the risk associated with hypertension was higher among users of these medications than among non-users. The difference may reflect a higher prevalence of more severe hypertension among users of these medications. In addition, it is also possible that hypertension was underreported among non-users. Alternatively, there may be unidentified risk factors for the cancers that predispose to both hypertension and use of medications, thus indirectly increasing the risk associated with a history of hypertension and drug use.

Our findings raise the possibility that hypertension may predispose not only to renal cell cancer, as previously reported, but also to tumors of the renal pelvis and ureter. Although the mechanisms are obscure, it is noteworthy that vasoactive substances (including certain protooncogenes, angiotensin II and other growth factors) are involved in hypertension (Naftilan *et al.*, 1990; Neyses and Vetter, 1992). A similar mechanism may contribute to the development of renal cell cancer (Volm *et al.*, 1993; Stumm *et al.*, 1996) and perhaps to renal pelvis and ureter cancers and thus deserves further study. We considered the possibility that hypertension may be a consequence of the renal tumor or associated conditions of the urinary tract, including reflux nephropathy (Preston *et al.*, 1996; Goonasekera *et al.*, 1996), but this seems unlikely because we excluded diagnoses within 5 years of interview.

Some epidemiologic studies of renal pelvis cancers have suggested a relation to preexisting conditions of the urinary tract,

including stones and infections, but the results have been equivocal. Risk estimates ranging from 1.2 to 1.7 for these conditions have been reported, with some reaching statistical significance (Ross *et al.*, 1989; McCredie and Stewart, 1992). The non-significant risk estimates in our study, ranging from 0.8 to 1.5, may reflect the exclusion of recent diagnoses from the analysis. The reasons for the non-significant, less-than-1 OR associated with a history of diabetes (OR = 0.6; 95% CI, 0.4–1.1) are not clear, although the diagnosis of diabetes, unexpectedly, was not correlated with the history of hypertension ($r = 0.16$) in our study.

The strengths of our study include the use of population-based cancer registries for case identification and of population-based controls. This approach helped minimize potential selection bias because all subjects were from the same study base (Wacholder *et al.*, 1992). In addition, the large sample size provided greater statistical power and permitted stratified analyses to clarify the relationships among hypertension, medications, and cancers of the renal pelvis and ureter. High-quality data resulted from a detailed assessment of medications and urinary tract and cardiovascular conditions by specially trained interviewers, along with exclusion of next-of-kin interviews.

Potential limitations of our study include the absence of validation of medical conditions and medications. Cases may be more likely to recall prior medical conditions and use of medications, resulting in an overestimation of risks. Apart from hypertension, however, no associations were observed for previous medical conditions or other medications in our study. Survival bias due to the exclusion of deceased or severely ill subjects is possible, because those who survived until interview were perhaps less likely to suffer from various medical conditions or to use medications than those who did not survive. In addition, because refusal

was one of the major reasons for not being interviewed, the possibility that the subjects not interviewed may be different from those interviewed with respect to their medical conditions and use of medications cannot be excluded. However, the comparison between respondent and non-respondent cases suggested that they were comparable on the demographic characteristics that could be assessed. Because information on controls not interviewed was unavailable, comparisons could not be made between interviewed and non-interviewed controls.

In summary, the findings from our case-control study suggest that the association previously reported between hypertension and renal cell cancer may extend to cancers of the renal pelvis and ureter. Further epidemiologic and experimental studies of renal cancer by subsite are needed to distinguish between the effects of hypertension and antihypertensive drugs and to identify the carcinogenic mechanisms that may be involved.

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