

Cigarette Smoking and Cancers of the Renal Pelvis and Ureter

Joseph K. McLaughlin,¹ Debra T. Silverman, Ann W. Hsing, Ronald K. Ross, Janet B. Schoenberg, Mimi C. Yu, Annette Stemhagen, Charles F. Lynch, William J. Blot, and Joseph F. Fraumeni, Jr.

Epidemiology and Biostatistics Program, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland 20892 [J. K. M., D. T. S., A. W. H., W. J. B., J. F. F.]; Department of Preventive Medicine, University of Southern California School of Medicine, Los Angeles, California 90033 [R. K. R., M. C. Y.]; New Jersey Department of Health, Trenton, New Jersey 08625 [J. B. S., A. S.]; and Department of Preventive Medicine and Environmental Health, University of Iowa College of Medicine, Iowa City, Iowa 52242 [C. F. L.]

ABSTRACT

A population-based case-control study of renal pelvis and ureter cancers (502 cases, 496 controls) conducted in three areas of the United States found cigarette smoking to be associated with a 3.1-fold increase in risk, with long-term (>45 years) smokers having a 7.2-fold increased risk. Statistically significant dose-response associations were observed for both cancer sites and in both sexes regardless of the measure used: cigarettes per day, duration of use, or pack years. A significant decreasing trend in risk with increasing years quit smoking was also demonstrated for these cancers. Attributable risk estimates indicate that approximately 7 of 10 cancers of the renal pelvis and ureter among men and almost 4 of 10 among women are caused by smoking. The results of this study, the largest to date, confirm that cigarette smoking is the major cause of cancers of the renal pelvis and ureter, and that cessation of smoking could eliminate a large proportion of these tumors.

INTRODUCTION

Cancers of the renal pelvis and ureter account for approximately 8% of the malignant tumors arising in the urinary tract (1). Although relatively rare, these cancers are increasing at a rate of 3% per year (1). The major risk factor for these predominantly transitional cell neoplasms is cigarette smoking, with attributable risk estimates ranging from 56 to 82% among men and from 40 to 62% among women (2, 3). Previous case-control studies of cancers of the renal pelvis and ureter have usually reported much higher smoking-related risks than those reported for bladder cancer or for renal cell cancer, the predominant tumors of the urinary tract (4). To further evaluate cigarette smoking and a number of other exposures, we conducted a case-control study of renal pelvis and ureter cancers in three areas of the United States. While most of the previous studies of these cancers involved fewer than 100 cases, the present investigation of 502 cases and 496 controls is the largest to date for these rare tumors, and provides an opportunity to examine the role of cigarette smoking in detail. Herein we report our findings.

MATERIALS AND METHODS

Cases were defined as any individual 20 to 79 years of age living in the states of New Jersey and Iowa or in Los Angeles County, California, newly diagnosed with microscopically confirmed cancers of the renal pelvis (ICD 9:189.1) or ureter (ICD 9:189.2) between January 1, 1983 and December 31, 1986. Cases were identified by using the population-based cancer registries of the three areas. Ascertainment began in late 1985, with cases identified both retrospectively and prospectively in the three registries. As there were few cases of these rare tumors among nonwhites, the study was limited to whites. In each area, population-

based controls under the age of 65 were selected by using RDD² (5), and controls age 65 and older were selected from HCFA rosters (6). Controls were frequency matched to cases on age (5-year groups) and sex. Interviews were conducted in the homes of the subjects by trained interviewers. Every effort was made to blind the interviewers to the case or control status of the respondents. There were no next-of-kin interviews. The standardized questionnaire sought information in a structured manner on demographic background, tobacco history, use of prescription and over-the-counter medications, medical history, diet, and occupation. Any changes in smoking habits within 5 years of the interview were excluded from the analysis.

The OR was used as the measure of association between cancers of the renal pelvis and ureter and cigarette smoking (7). Summary ORs to adjust for the effect of other variables were calculated by using the maximum likelihood method with 95% confidence intervals derived from Gart's modification of Cornfield's method (8). All ORs were adjusted for age, study area, and, where appropriate, for sex. Potential confounding by marital status, analgesic use (the only other reasonably well-established risk factor for these cancers), and education was examined and found to have no effect on the association with cigarette smoking. The test for linear trend (one-tailed) was the Mantel extension of the Mantel-Haenszel procedure (9). Population attributable risk percentages were computed by using the method described by Whittemore (10). The categories for years smoked and pack years were determined by dividing the study subjects who smoked into quartiles.

RESULTS

Interviews were obtained for 502 cases (308 renal pelvis cancers and 194 ureter cancers) and 496 controls. This represents 58% of the ascertained cases, 54% of the RDD controls, and 66% of the HCFA controls. Among the cases, the major reasons for noninterviews were death or illness (215 or 25%) and physician or subject refusals (95 or 11%). For the RDD controls the response rate at the household screening phase was 92%, but 59% at the interview phase. The major reasons for nonresponse among RDD controls at the interview phase were refusals (71 or 23%) and untraceable respondents and language problems (38 or 13%). The major reasons for nonresponse among HCFA controls were refusals (76 or 16%), death or illness (34 or 7%), and untraceable respondents and language problems (40 or 8%). An examination of the age, sex, and cancer site distribution of the noninterviewed cases showed them to be similar by sex and cancer site, but slightly older than those interviewed. For the cancers included in the analysis, 97% were transitional cell tumors and 3% were squamous cell or papillary cancers.

Table 1 shows the risks associated with cigarette smoking by cancer site and sex. Among men with renal pelvis cancer, ever smokers had a 3.9-fold increased risk, current smokers had a 6.5-fold increased risk, and former smokers a 2.6-fold risk. Strong and significant dose-response relationships were seen for amount smoked per day, years smoked, and pack years of

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¹To whom requests for reprints should be addressed, at National Cancer Institute, Executive Plaza North, Room 415, Bethesda, MD 20892.

²The abbreviations used are: RDD, random digit dialing; HCFA, Health Care Financing Administration; OR, odds ratio.

Table 1 ORs and 95% confidence intervals (CI) for cancers of the renal pelvis and ureter for cigarette smoking by cancer site

Cigarette Smoking Status	Renal pelvis cancer						Ureter cancer							
	Men (193; 315) ^a		Women (115; 181)		Both sexes (308; 496)		Men (138; 315)		Women (56; 181)		Both sexes (194; 496)		Total (502; 496)	
	OR ^b	95% CI	OR ^b	95% CI	OR ^c	95% CI	OR ^b	95% CI	OR ^b	95% CI	OR ^c	95% CI	OR ^c	95% CI
No tobacco use	1.0													
Ever smokers	3.9	2.1-7.3	2.0	1.2-3.5	2.7	1.8-4.1	5.2	2.4-11.9	3.1	1.4-7.0	4.1	2.4-7.1	3.1	2.2-4.4
Current smokers	6.5	1.2-12.7	2.4	1.3-4.3	3.8	2.4-5.9	11.4	4.4-31.5	4.1	1.7-10.2	6.9	3.7-13.1	4.4	2.9-6.5
Former smokers	2.6	1.3-5.2	1.6	0.8-3.3	2.0	1.3-3.4	3.4	1.5-7.9	2.0	0.7-5.6	2.7	1.5-5.1	2.3	1.5-3.4
Cigarette/day														
<20	3.2	1.4-7.2	1.4	0.7-3.0	2.1	1.3-3.5	5.6	2.0-16.0	2.4	0.9-6.4	3.7	1.9-7.2	2.4	1.6-3.8
20-39	3.8	1.9-7.6	2.7	1.4-5.2	3.2	2.0-5.1	5.4	2.3-13.1	4.2	1.6-11.3	4.8	2.6-9.2	3.6	2.4-5.4
40+	5.1	2.4-10.9	3.4	0.9-13.4	4.6	2.4-8.8	7.7	2.6-24.7	3.7	0.4-38.9	6.7	2.6-17.8	4.8	2.7-8.5
(P for trend) ^d	(<0.001)		(<0.001)		(<0.001)		(<0.001)		(<0.001)		(<0.001)		(<0.001)	
Years smoked														
<26	2.4	1.1-5.5	0.9	0.3-2.2	1.6	0.9-2.8	3.0	1.1-8.5	0.8	0.2-3.5	1.9	0.9-4.2	1.7	1.0-2.8
26-37	3.1	1.5-6.7	1.4	0.6-3.4	2.2	1.3-3.9	4.6	1.7-12.6	1.7	0.5-6.3	3.2	1.5-6.8	2.5	1.6-4.1
38-45	4.7	2.1-10.7	2.2	1.0-4.9	3.2	1.8-5.6	5.1	1.9-14.4	5.2	1.5-18.7	5.1	2.4-11.2	3.6	2.2-5.9
46+	5.9	2.6-13.7	7.9	2.8-22.6	6.6	3.5-12.6	9.9	3.5-30.0	8.9	2.5-33.4	9.5	4.3-21.5	7.2	4.1-12.6
(P for trend) ^d	(<0.001)		(<0.001)		(<0.001)		(<0.001)		(<0.001)		(<0.001)		(<0.001)	
Pack-years														
1-20	3.0	1.3-6.7	1.1	0.5-2.5	1.8	1.1-3.2	4.3	1.4-13.6	1.0	0.3-3.4	2.3	1.1-4.8	2.0	1.2-3.2
21-38	4.1	1.8-9.4	1.7	0.8-3.8	2.7	1.5-4.6	7.0	2.7-18.8	3.9	1.2-12.4	5.6	2.7-11.4	3.3	2.1-5.3
39-59	3.1	1.4-6.8	3.0	1.3-7.1	3.1	1.8-5.4	5.8	2.2-15.8	6.3	2.1-19.6	6.0	3.0-12.4	3.8	2.4-6.2
60+	5.9	2.8-12.6	7.8	2.2-29.8	6.4	3.4-12.1	7.3	2.7-20.6	6.4	0.5-100.0	7.1	2.9-18.3	6.2	3.5-10.8
(P for trend) ^d	(<0.001)		(<0.001)		(<0.001)		(<0.001)		(<0.001)		(<0.001)		(<0.001)	

^a Total number of cases; controls in parentheses. Subjects with missing information and exclusive cigar and pipe smokers are excluded from analysis.

^b Adjusted for age and study area.

^c Adjusted for age, sex, and study area.

^d One-sided.

cigarette use. Among women, ever smokers had a 2.0-fold increased risk, current smokers had a 2.4-fold risk, and former smokers a 1.6-fold risk. As did men, women had strong and significant trends in risk for amount smoked per day, years smoked, and pack-years of use.

In general, the smoking-related risks were higher for ureter cancer than for renal pelvis cancer (Table 1). For ureter cancer, cigarette smoking among men was associated with ORs of 5.2, 11.4, and 3.4 for ever, current, and former smokers, respectively. Dose-response trends for amount, years smoked, and pack-years of use were strong and highly significant. Among women, the risk of ureter cancer was increased 3.1-fold for ever smokers, 4.1-fold for current smokers, and 2.0-fold for former smokers. Dose-response gradients were statistically significant among women for cigarettes smoked per day, years smoked, and pack-years of use, although for cigarettes smoked per day and pack-years of use the trends were not as consistent as that observed for duration of smoking.

When data from both cancer sites and sexes are combined (Table 1, last column), current cigarette smokers had over a 4-fold risk for these tumors, with heavy smokers having 5- to 7-fold risks, depending on the smoking variable examined.

Table 2 presents results by amount smoked and duration for renal pelvis and ureter cancers, which indicate that within each category of cigarettes smoked per day a rising risk can be seen with increasing years of smoking. In general, within each category of years smoked there was also an increasing risk with amount smoked, although amount smoked had little impact on risk among those who smoked the longest (>45 years). In general, duration appeared to be a stronger indicator of risk than amount smoked.

An effect of quitting cigarette smoking was observed for both renal pelvis and ureter cancers, with risks decreasing as years quit increased (Table 3). Those quitting 10 or more years had

approximately a 60-70% reduction in risk, relative to current smokers. Risk of renal pelvis and ureter cancers was much lower for those starting to smoke at age 25 or older, compared with subjects who started at age 14 or younger (Table 3). Because duration of smoking is a function of age started and age at diagnosis for current smokers, and a function of age started, age quit, and age at diagnosis for former smokers, independent effects of duration, age started or years quit could not be disentangled.

We inquired whether subjects usually smoked unfiltered, filtered or both types of cigarettes. There was little difference in risk between those who smoked filtered compared with unfiltered cigarettes. Risks associated with depth of inhalation varied little among light, moderate, or deep inhalers, relative to those who did not inhale. Risks for the small number of men (12 cases; 21 controls) who smoked only cigars or pipes were elevated but not significantly for either renal pelvis cancer (OR = 1.9; 95% confidence interval: 0.6-6.4) or ureter cancer (OR = 1.4; 95% confidence interval: 0.3-6.4).

Table 4 presents the population attributable risk percentage by cancer site and sex. Seventy % of the cancers among men and 37% among women can be ascribed to smoking in this study population. The age-, sex-, and study area-adjusted pop-

Table 2 ORs and 95% confidence intervals (CI) for cancers of the renal pelvis and ureter by number of cigarettes per day and years smoked

Cigarettes/day	Years smoked							
	<26 years		26-37 years		38-45 years		>45 years	
	OR ^a	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
1-19	1.3	0.7-2.5	2.1	1.0-4.4	3.8	1.8-8.1	6.1	2.5-15.3
20-39	2.1	1.1-4.0	3.2	1.7-6.1	3.0	1.6-5.6	7.5	3.9-14.7
40+	3.8	1.2-11.7	3.0	1.4-6.7	7.7	3.0-20.7	6.7	2.5-18.3

^a ORs are relative to subjects who never used tobacco and are adjusted for age, sex, and study area.

Table 3 ORs and 95% confidence intervals (CI) for cancers of the renal pelvis and ureter for time since quitting and age started cigarette smoking by cancer site and sex

	Renal pelvis cancer						Ureter cancer							
	Men		Women		Both sexes		Men		Women		Both sexes		Total	
	OR ^a	95% CI	OR ^a	95% CI	OR ^b	95% CI	OR ^a	95% CI	OR ^a	95% CI	OR ^b	95% CI	OR ^b	95% CI
Years quit														
Current smoker ^c	1.0		1.0		1.0		1.0		1.0		1.0		1.0	
<10	0.5	0.1-1.6	1.1	0.3-4.2	0.7	0.3-1.7	0.7	0.2-2.7	1.6	0.3-9.9	1.0	0.4-2.7	0.9	0.4-1.8
10-24	0.3	0.2-0.6	0.4	0.1-1.2	0.4	0.2-0.6	0.3	0.1-0.6	0.4	0.1-1.6	0.3	0.2-0.6	0.3	0.2-0.5
≥25	0.2	0.1-0.6	0.7	0.1-4.7	0.3	0.1-0.6	0.2	0.1-0.6	0.4	0.0-6.9	0.3	0.1-0.6	0.3	0.2-0.5
(P for trend) ^d	(<0.001)		(0.10)		(<0.001)		(<0.001)		(0.12)		(<0.001)		(<0.001)	
Age started														
≤14	1.0		1.0		1.0		1.0		1.0		1.0		1.0	
15-24	1.2	2.3-8.4	1.0	0.1-7.4	1.2	0.6-2.1	1.0	0.5-1.9	0.7	0.1-8.9	0.9	0.5-1.8	1.1	0.7-1.8
≥25	0.4	0.7-6.6	0.4	0.0-7.2	0.5	0.1-1.7	0.2	0.0-0.9	0.1	0.0-4.9	0.1	0.0-0.7	0.3	0.1-0.9
(P for trend) ^d	(0.10)		(0.002)		(0.008)		(0.023)		(0.021)		(0.004)		(0.002)	

^a Adjusted for age, study area, and amount smoked per day.
^b Adjusted for age, sex, study area, and amount smoked per day.
^c Includes individuals who quit within 5 years of the interview.
^d One-sided.

ulation attributable risk percentage were higher for ureter cancer (63%) than for renal pelvis cancer (48%).

DISCUSSION

This large, population-based study of cancers of the renal pelvis and ureter demonstrates that these tumors are mainly induced by cigarette smoking. The results are consistent with the 8 previous case-control studies of cancers of the renal pelvis and ureter conducted in the United States (2, 11, 12), England (13), Denmark (3), and Australia (14-16). In these studies, the risks among heavy smokers ranged from 4- to 11-fold, relative to nonsmokers. In two studies attributable risks of cigarette smoking were estimated to be 56 to 82% for men and 40 to 62% for women (2, 3). The results for our study population, 70% for men and 37% for women, are consistent with the earlier investigations.

An effect of smoking cessation on cancers of the renal pelvis and ureter was shown in this study. The decline in risk was consistent in both men and women only after 10 years of cessation, when a 60 to 70% reduction in risk relative to current smokers was observed. This sharp decline in risk suggests that smoking affects a relatively late stage in renal pelvis and ureter carcinogenesis, and offers promise that programs aimed at smoking cessation will have a beneficial effect on lowering risk of these cancers. It was not possible to establish independent effects for years quit and duration, however, as they were highly correlated. In a large case-control study (2982 cases; 5782 controls) of bladder cancer, the predominant transitional cell cancer of the urinary tract, independent effects for quitting and duration of smoking have been reported (17), supporting the possibility that the effects seen here for cancers of the renal pelvis and ureter are also independent.

Risks observed for ureter cancer were generally higher than those seen for renal pelvis cancer, which is consistent with findings from a recent case-control study of these tumors (12). The reason for the higher smoking-related risks for ureter cancer is not clear, although the observed risks were not significantly different. It is also not known why the odds ratios among smokers for both renal pelvis and ureter cancers are higher than for bladder cancer. Cigarette smoke contains a large number of carcinogens that may affect all parts of the urinary tract (18). Future research should clarify whether exposure to

Table 4 Population attributable risk (PAR) percentage and 95% confidence interval (CI) for smoking by cancer site and sex

Sex	Renal pelvis cancer		Ureter cancer		Total	
	PAR ^a	95% CI	PAR	95% CI	PAR	95% CI
Men	67	47-82	70	45-87	70	54-82
Women	31	13-59	46	22-72	37	20-58
Both	48	33-64	63	46-77	54	42-66

^a Adjusted for age, study area, and sex.

carcinogens is more concentrated in the renal pelvis and ureter than the bladder, where dilution or degradation of tobacco-related carcinogens may occur, or whether the epithelium of the renal pelvis and ureter may be especially susceptible to carcinogens.

In summary, this large-scale, population-based case-control study of cancers of the renal pelvis and ureter provides convincing evidence that cigarette smoking accounts for the majority of these cancers, and that cessation of smoking would eliminate them to a large extent.

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