

Exhibit 217

Occupational risk factors for renal cell carcinoma: a case-control study

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Abstract

A case-control study of 196 histologically proved cases of renal cell carcinoma and 347 controls matched for age at interview, sex, hospital, and interviewer was conducted in France between 1987 and 1991. A complete occupational history was recorded for each patient and occupations were coded blindly according to the International Standard Classification of Occupations. In women, none of the risks were significant. Among men, after adjustment for the educational level, cigarette smoking, and Quetelet index before diagnosis, significantly increased matched odds ratios (ORs) were found for sales workers (OR = 2.1, 95% confidence interval (95% CI) 1.2-4.0), managers (OR = 3.3, 95% CI 1.2-8.9), and textile workers and tailors (OR = 6.2, 95% CI 1.1-33.7). For this last occupational group, an increase in risk was found with an increased duration of exposure.

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Cancers of the urinary tract were the subject of a recent descriptive epidemiological study.¹ These cancers account for 7% of all those diagnosed. The most common site within the urinary tract among white patients in the United States is the bladder (69%). Cancers of the renal parenchyma (23%), the renal pelvis (5%), the ureter (3%), and the urethra (1%) occur less often.

Little is known about the aetiology of renal cell carcinoma, but tobacco smoking and obesity seem to be the most consistently reported risk factors. The occupational determinants of renal cancer are poorly understood, but the fact that several agents have a carcinogenic effect on the kidney in laboratory animals suggests that cancer of the kidney might be associated with some occupational agents. Several substances, occupations, and industries have been associated with an increased risk of kidney cancer including cadmium,² asbestos,^{3,4} tar and pitch products,⁵ petroleum related workers,⁵⁻⁸ coke oven workers,⁹ truck drivers,¹⁰ newspaper pressmen,¹¹ printing industry,⁸ laundry and dry cleaning,^{7,12,13} and metal manufacturing.⁸ A suggestion of an association was also reported for tanners¹⁴ and textile workers.¹⁵ At present, however, coke and cadmium are the only two carcinogens causally or potentially related to renal cancer.¹⁶ Lastly, an

increased risk of renal cancer was also reported among white collar workers.^{8,17}

We report here the results of a case-control study conducted in France from 1987 to 1991 on 196 cases of renal cell carcinoma.

Materials and methods

The design of the study has been reported previously.¹⁸ Data were collected in 10 hospitals and were obtained from 138 men and 58 women with a histologically proved renal cell carcinoma.

Each case was matched for sex, age at interview (within five years), hospital, and interviewer with two controls (one control with a malignant disease and one with a non-malignant disease) admitted to hospital for a non-tobacco related disease. Patients with alcoholic cirrhosis or diabetes were not included. One hundred and fifty one cases were matched to two controls and the other 45 cases to one control only. This was due to difficulties in recruitment because of the matching and eligibility criteria. In all, 161 controls with cancer (107 men and 54 women) and 186 controls with non-malignant disease (128 men and 58 women) were included. Participation was almost complete, as only one case and two controls approached for interview refused to participate. Information was collected from the study participants during the course of their stay in hospital with a standardised questionnaire used by trained interviewers. The questionnaire included questions about the educational level, height, weight at two time points, smoking habits, consumption of beverages, and certain types of medication. A complete occupational history was recorded. Respondents were asked to indicate their occupational history (from the most recent to the first occupation) and the duration at each position (at least one year). Interviewers were aware of the case or control state, but the data were coded blindly with the International Standard Classification of Occupations.¹⁹

ANALYTICAL METHODS

Data were validated by the PIGAS system.²⁰ Conditional logistic regression²¹ was used to estimate the odds ratio (OR) of renal cell cancer and the 95% confidence intervals (95% CIs). Analyses were performed separately for men and women. The matched ORs are implicitly adjusted for the matching variables age, hospital, and interviewer. Moreover, adjustments for the educational

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Table 1 Adjusted matched ORs of renal cell carcinoma for major groups of occupations*

	Men			Women		
	No of cases	No of controls	Matched OR† (95% CI)	No of cases	No of controls	Matched OR† (95% CI)
Professional, technical, related workers (011-199)	43	58	1.1 (0.6-2.0)	9	20	0.5 (0.2-1.4)
Administrative and managerial workers (201-219)	19	14	2.3 (1.0-5.4)	0	0	—
Clerical and related workers (300-399)	24	39	1.2 (0.7-2.1)	22	28	1.6 (0.7-3.5)
Sales workers (400-490)	29	32	2.1 (1.2-4.0)	8	13	1.4 (0.5-3.7)
Service workers (500-599)	12	36	0.4 (0.2-1.0)	4	27	0.3 (0.1-0.8)
Agricultural, animal husbandry, and forestry workers, fishermen, and hunters (600-649)	20	37	1.2 (0.6-2.3)	4	8	1.5 (0.4-6.3)
Production and related workers, transport equipment operators, and labourers (700-999)	52	110	0.8 (0.5-1.3)	13	31	0.7 (0.3-1.7)

*Groups classified according to the International Standard Classification of Occupations (ISCO, 1968).

†Adjusted for number of years at school (≤ 4 , 5-7, 8-10, ≥ 11), smoking state (non-smokers, ever smokers), and Quetelet index before diagnosis (≤ 20 , 21-23, 24-26, ≥ 27).

level, cigarette smoking, and the Quetelet index before diagnosis were done. The occupations studied were similarly distributed between the two series of controls. The analyses were conducted in each control group for major groups of occupations. As similar results were obtained for both control groups in women and in men, only the matched analysis with the pooled control groups is given here. A result was considered non-significant (NS) when its associated p value was above 0.05.

Results

For each occupation of interest, the baseline category was composed of patients who had never been engaged in that particular occupation. Table 1 shows the matched OR of renal cell carcinoma for major groups of occupations, adjusted for the educational level, exposure to cigarettes, and the Quetelet index. In men, a significant excess risk of renal cell cancer, or one of borderline significance, was found for sales workers (OR = 2.1, 95% CI 1.2-4.0), and for administrative and managerial workers (OR = 2.3, 95% CI 1.0-5.4). By contrast, the lower risk for service workers was of borderline significance (OR = 0.4, 95% CI 0.2-1.0). None of the risks were significantly increased among women. A significant decreased risk was found for service workers (OR = 0.3, 95% CI 0.1-0.8). There was no evidence of an increase in risk with the duration of exposure for any major occupational group, neither in men nor in women.

A more detailed analysis was performed for occupations either including at least 10 cases or controls or both or previously reported to be associated with renal cancer in men (table 2) and in women (table 3). In men, a significant 3.3-fold risk (95% CI 1.2-8.9) of renal cell carcinoma was found for managers. Because of the small number of men working in the textile industry, and of tailors and related workers, these two occupational groups were pooled, and a significantly increased risk was found (OR = 6.2, 95% CI 1.2-33.7). Moreover, evidence indicated an increase in risk with the duration of exposure: the risk for renal cell cancer was 1.7 (95% CI 0.1-21.8) after 10 years or less of exposure and 12.9 (95% CI 1.4-120.1) after more than 10 years of exposure (trend test $p = 0.02$). Risks associated with other occupational groups were mostly close to one and there was no evidence of an increase in risk with the duration of exposure. As the number of women involved in the study (58 cases and 112 controls) was rather small and because about 20% of women had no occupation, the analyses were restricted to fewer occupational groups than for men. None of the risks were significantly increased (table 3).

Table 2 Adjusted matched ORs for renal cell carcinoma for some occupations* in men

	No of cases	No of controls	Matched OR† (95% CI)
Architects, engineers, and related workers (021-039)	22	24	1.4 (0.7-2.8)
Life scientists, medical, dental, veterinary, and related workers (050-079)	4	11	0.4 (0.1-1.4)
Teachers (131-139)	6	9	1.0 (0.3-3.2)
Managers (210-219)	17	8	3.3 (1.2-8.9)
Cooks, waiters, bartenders, and related workers (531-532)	2	13	0.2 (0.0-1.1)
Protective service workers (580-589)	3	10	0.4 (0.1-1.7)
Farmers, agricultural and animal husbandary workers (611-629)	18	36	1.0 (0.5-2.0)
Forestry workers, cabinet makers, and related woodworkers (631-632, 811, 812, 819)	4	6	0.7 (0.2-3.2)
Textile workers and tailors (750-759, 791-799)	6	3	6.2 (1.2-33.7)
Blacksmiths, toolmakers, and machine tool operators (830-839)	7	12	1.5 (0.5-4.5)
Machinery fitters, machine assemblers, and precision instrument makers (841-849)	8	16	0.7 (0.3-1.9)
Electrical fitters and related electrical and electronics workers (851-859)	4	10	0.8 (0.2-2.5)
Plumbers, welders, sheet metal, and structural metal preparers and erectors (871-874)	2	7	0.6 (0.1-3.6)
Bricklayers, carpenters, and other construction workers (951-959)	8	21	0.9 (0.3-2.1)
Transport equipment operators (981-989)	4	14	0.5 (0.2-1.6)

*Groups classified according to the International Standard Classification of Occupations.¹⁸

†Adjusted for number of years at school (≤ 4 , 5-7, 8-10, ≥ 11), smoking state (non-smokers, ever smokers) and Quetelet index before diagnosis (≤ 20 , 21-23, 24-26, ≥ 27).

Table 3 Adjusted matched ORs for renal cell carcinoma for some occupations* in women

	No of cases	No of controls	Matched OR† (95% CI)
Teachers (131-139)	6	6	1.6 (0.4-6.5)
Building caretakers, charworkers, cleaners, and related workers (551-552)	2	10	0.4 (0.1-2.3)
Farmers, agricultural and animal husbandry workers (611-629)	4	8	1.5 (0.4-6.3)
Textile workers and tailors (750-759, 791-799)	7	14	0.9 (0.3-2.6)

*Groups classified according to the International Standard Classification of Occupations.¹⁹

†Adjusted for number of years at school (≤ 4 , 5-7, 8-10, ≥ 11), smoking state (non-smokers, ever smokers) and Quetelet index before diagnosis (≤ 20 , 21-23, 24-26, ≥ 27).

Discussion

The associations between renal cell carcinoma and some occupations found in this study are consistent with those previously reported. In one study,¹⁷ there was a significantly increased risk for male white collar administrative workers. Our study also showed a significant twofold risk for this occupational group, and within this group a significant 3·3-fold risk for managers. In another study,⁸ the risk was also about twofold for white collar occupations considered as a whole. Likewise, in our study a significant twofold risk was found for male sales workers. This result is in agreement with that reported previously.¹⁷ The over-representation of non-manual workers among the cases reflects a higher educational level among cases than among controls in our study. Even after adjustment for the educational level, however, the risks of renal cancer were increased among white collar workers. As non-manual workers are less exposed to toxic agents than manual workers, and because the most consistently reported risk factors of renal cell cancer (smoking and obesity) were taken into account in the analyses, other lifestyle habits than those recorded in this study may account for the associations found here.

Male textile workers and tailors had a significant 6·2-fold excess risk of renal cell carcinoma. This result corroborates previous findings that showed a higher proportion of men who had worked with textiles among cases than among controls.¹⁵ Whereas the number of female textile workers was greater than that of male workers, the risk was not significantly different from unity in female workers. This result could be explained by the greater duration of exposure in male cases (26 years) than in male controls (18 years), whereas the duration of exposure was the same in female cases and in female controls (15 years). By contrast, a significant threefold risk of renal cell cancer was found for truck drivers in one study¹⁰ but not in ours. Similarly, a significant decreased risk was found for agricultural workers in two studies,⁸ but this result was not confirmed in another study,²² nor in ours.

The relative risks of renal cell carcinoma previously reported to be increased^{5-9,12-14} among certain other occupational groups (petroleum refining workers, printing, laundry workers, oven workers, and tanners) could not be estimated in this study because the number of cases and controls for each occupational category was too small. As only occupations were recorded in this study, it was not possible to evaluate the risks related to a specific exposure to substances such as asbestos, cadmium, coke, tar, or pitch. As the reference category used to study a given occupation included people potentially exposed to other toxic substances it is likely that some negative results may reflect an underestimation of the risks.

Despite these reservations, and the negative results of several studies investigating relations between renal cell cancer and occupations,²²⁻²⁵ the present study provides a certain

amount of evidence that some occupations, as well as smoking and obesity, could be related to this cancer.

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