Exhibit 275

Occupational Risk Factors for Renal Cell Cancer: A Case–Control Study in Northern Italy

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Relatively little is known about occupational and other risk factors for renal-cell carcinoma (RCC). Associations between RCC and occupations, exposures and other factors were investigated in a hospital-based case-control study in Bologna (central-northern Italy). Between 1986 and 1994, 324 histologically confirmed RCC cases were diagnosed at Policlinico S. Orsola-Malpighi in patients from the Province of Bologna. Corresponding control subjects admitted to the same hospital with any diagnosis except RCC were matched for sex, age, and residency. We studied the 249 cases and 238 controls for whom detailed information on occupational history, diet, smoking habits, alcohol and drug intake was obtained. At conditional logistic regression, among males (167 matched pairs), significant matched odds ratios (OR) were found, after adjusting for cigarette smoking and alcohol intake, for high body-mass index BMI (third quartile: OR, 4.91; confidence interval [95% CI], 1.56–15.5; last quartile: OR, 4.42; 95% CI, 1.48–13.18), railway workers (OR, 10.14; 95% CI, 1.46–70.17) and asbestos exposure (OR, 7.11; 95% CI, 1.46–34.51); nearly significant OR were found for managers (OR, 3.59; 95% CI, 0.82–15.59) and metal workers (OR, 2.21; 95% CI, 0.99–5.37). Among females (52 pairs), significant OR were found for BMI >25.4 (OR, 8.46; 95% CI, 1.02–68.0). Railway workers (on or near to trains) may have increased risk of developing RCC, possibly due to asbestos exposure. Studies are required on possible risks encountered by railway (and metal) workers and by managers. (J Occup Environ Med. *2002;44:1028–1036*)

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Cancer of the renal parenchyma, generally known as renal-cell carcinoma (RCC), is the most common form of kidney cancer, accounting for about 23% of all diagnosed cancers of the urinary tract. RCC is a numerically important cancer (representing 7% of all diagnosed cancers), and its incidence has risen, during the last few decades, especially in industrialized countries.[1] The upward incidence trend of RCC cannot be entirely explained by the increased detection of presymptomatic tumors thanks to imaging procedures such as ultrasound, computed tomography and magnetic resonance imaging;[2] other contributing factors await identification. Despite various epidemiological studies, however, the etiology of RCC remains largely unknown.[3]

The incidence of RCC varies considerably among different populations and states. For example, in Sweden the standardized incidence rate among males is about 10 cases per 100,000 persons per year, whereas in Costarica the figure is about three times lower. In Los Angeles, the Chinese have the lowest incidence of any ethnic group, but this is still higher than that recorded among the inhabitants of Shanghai.[4] Thus, dietary, environmental and occupational factors seem to exert an important pathogenetic influence on RCC.[5]

Although, with the exception of occupational exposure to asbestos, RCC was once not generally considered a "work-related" disease,[6] in 1995, the International RCC Study concluded that “occupation may play a larger role in the etiology of RCC than previously thought.” Indeed, this report provided important confirmation of some previously suggested occupational risk factors, such as employment in the metal industry, and exposure to cadmium, dry-cleaning solvents, or petroleum products. To search for further information about possible risk factors for RCC, we designed a hospital based case-control study in a strictly defined geographical area.

Methods

This hospital-based case-control study regarded the 324 RCC patients resident in Bologna and its Province who were registered at the University hospital of Bologna, *Policlinico Sant’Orsola-Malpighi*, from January 1987 to December 1994. In all cases, diagnosis of RCC was histologically confirmed by a reference pathologist (P.B.). The cases were matched 1:1 with 324 control subjects residing in the same geographical area, who admitted to the same hospital in 1991 with any diagnosis except RCC (this approximately half-way year was chosen for practical reasons based on the hospital’s archival convenience). The controls were matched on the basis of the following criteria: gender; age (to within 5 years); place of birth (ie, Northern, Central or Southern Italy; foreign countries); residence environment (ie, same urban district of Bologna, same cluster of small towns, same area of plain or hills).

The overall population of the city and province of Bologna is about 920,000. Bologna is not covered by a cancer register, and so rates of RCC could only be estimated on the basis of the rates of similar provinces nearby (Modena, Ferrara, Florence, Forlì, Cesena, and Rimini). Between 1989 and 1992, the average standardized rates of RCC, in these provinces ranged from 11.2 to 15.8 (per 100,000 persons per year) for males and from 5.4 to 6.2 for females. These are among the highest figures in Europe.[4]

We drew up a structured, written questionnaire, requesting specific information on height, weight, lifelong smoking habits, alcohol and coffee consumption (usual consumption per day), meat intake (portions usually eaten per week), use of phenacetin or of diuretics, and occupational history (profession, types of occupation, duration of stay in each job, qualitative description of the occupational exposures); all the information referred to the period before the diagnosis.

The questionnaire was posted to the addresses of all 648 subjects and telephone interviews were conducted in case of non-response by mail. When telephone contact also failed, the subject was classified as a non-respondent and was not substituted; in such cases, the corresponding matched patient/control pair was excluded from conditional logistic regression analysis and Cuzik’s test for trend. The telephone interviews were done blindly to case-control status by one trained interviewer, who filled in the questionnaire. For deceased subjects and those too ill to answer, the next of kin filled in the questionnaire or replied by phone. All respondents had received prior information on the nature of the study, which was promoted and approved by the Local Health Authority (U.S.L.).

Job titles were coded (following the European Union variant of International Standard Classification of Occupations—ISCO 88[7]) blindly to case-control status by three occupational physicians (S.M., D.T., A.R.). Occupational exposures were coded blindly by an industrial hygienist (B.M.). A subject was considered as having been exposed to a specific substance or as having a certain profession when the exposure or job lasted for at least 2 years. The job titles were coded and grouped blindly into 27 categories for males and 8 categories for females. “Certain/very probable” professional exposures were coded blindly into 8 categories for males (asbestos, petroleum products, solvents, mineral oils, welding fumes, foundry fumes, inorganic lead, and pesticides); other categories, such as ionizing radiation, were not analyzed because they regarded too few subjects. For females, only two “certain/very probable” professional exposures were coded (pesticides and solvents) due to the low prevalence of other categories. Height and weight were used to calculate body mass index (BMI) in Kg/m^2. An alcohol intake score was computed as the product of the alcohol equivalent (g/ml) in each type of drink and the volume of wine, beer, or spirits consumed each day.

All the 487 (75.2%) subjects who were successfully traced (249 RCC patients, 238 controls subjects) provided detailed responses to the questionnaire. Thus, responses were obtained from 219/324 (67.6%) of the matched pairs of RCC patients and controls.

Statistical Analysis

Analyses were performed separately for males and females. Odds ratios (OR) and 95% confidence interval (95% CI) were estimated by conditional logistic regression, according to Breslow and Day.[8] The matched OR were implicitly adjusted for the matching variables: age, gender, birthplace, and residence. For multivariate analysis, BMI, smoking, consumption of coffee, alcohol, phenacetin and/or of diuretics, and meat were introduced as categorical variables, while job titles and professional exposures were binary variables. The categorization and reference categories used in the models for males and females are shown in Tables 2 and 3, respectively. For job titles where a significant (or nearly significant) association with RCC was found, influence of duration of employment was assessed by a test for trend.[9] For all tests, the results were considered to be significant at $P < 0.05$. The STATA 6 software package was used for analysis.

TABLE 1
Types of Response Provided by 219 RCC Patients and 219 Matched Control Subjects and Main Characteristics of Cases and Controls

	RCC patients (cases)			Control subjects		
	Patients N (%)	Next of kin N (%)	Total N (%)	Patients N (%)	Next of kin N (%)	Total N (%)
Mailed questionnaire	68 (31.0)	7 (3.2)	75 (34.2)	86 (39.2)	8 (3.6)	94 (42.8)
Questionnaire by phone	108 (49.3)	36 (16.5)	144 (65.8)	72 (32.9)	53 (24.3)	125 (57.2)
Total	176 (80.3)	43 (19.7)	219	158 (72.1)	61 (27.9)	219
Age distribution	Males	Females	Total	Males	Females	Total
0–39	3 (1.8)		3 (1.3)	2 (1.2)	2 (3.8)	4 (1.8)
40–49	13 (7.8)	1 (1.9)	14 (6.4)	11 (6.6)	3 (5.8)	14 (6.4)
50–59	36 (21.5)	13 (25.0)	49 (22.3)	38 (22.8)	6 (11.5)	44 (20.1)
60–69	62 (37.1)	21 (40.4)	83 (38.0)	59 (35.3)	21 (40.4)	80 (36.5)
70–79	45 (27.0)	12 (23.1)	57 (26.0)	53 (31.7)	19 (36.6)	72 (32.9)
$>$ 80	8 (4.8)	5 (9.6)	13 (6.0)	4 (2.4)	1 (1.9)	5 (2.3)
Main occupations	Males	Females	Total	Males	Females	Total
Managers	13 (7.8)		13 (5.9)	4 (2.4)		4 (1.8)
Clerks	17 (10.2)	7 (13.5)	24 (11.0)	24 (14.4)	5 (9.6)	29 (13.2)
Sales workers	15 (9.0)		15 (6.9)	18 (10.8)	2 (3.9)	20 (9.1)
Other white-collar workers	11 (6.6)	3 (5.8)	14 (6.4)	11 (6.6)	5 (9.6)	16 (7.3)
Metal workers	22 (13.2)		22 (10.0)	13 (7.8)		13 (5.9)
Building workers	12 (7.2)		12 (5.5)	17 (10.2)		17 (7.8)
Railway workers	9 (5.4)		9 (4.1)	2 (1.2)		2 (0.9)
Motor vehicle drivers	9 (5.4)		9 (4.1)	9 (5.4)		9 (4.1)
Other blue-collar workers	38 (22.7)	6 (11.5)	44 (20.1)	46 (27.5)	10 (19.2)	56 (25.6)
Farmers	21 (12.5)	14 (26.9)	35 (16.0)	23 (13.7)	8 (15.3)	31 (14.2)
Housewives		18 (34.6)	18 (8.2)		19 (36.6)	19 (8.7)
Housemaids		4 (7.7)	4 (1.8)		3 (5.8)	3 (1.4)
Diagnosis at hospital admission		Total			Total	
Renal cell cancer		219 (100)			0 (0)	
Other neoplastic malignant diseases		0 (0)			63 (28.8)	
Cardiovascular diseases		0 (0)			73 (33.3)	
Other non neoplastic diseases		0 (0)			83 (37.9)	

Results

Descriptive Analysis

Among the 219 matched pairs of subjects for whom replies were obtained, the modality of response was similar among RCC patients and control subjects (Table 1). The 219 control subjects were mostly admitted to hospital for non-malignant diseases (156 cases), including vascular and heart disorders (57 and 16 cases, respectively). The RCC patients and controls both reported similar numbers of jobs (1.71 $\pm$ 0.72 [range 1–3] among female RCC patients versus 1.53 $\pm$ 0.64 [range 1–3] among female control subjects; 1.82 $\pm$ 0.77 [range 1–5] among male RCC patients versus 1.84 $\pm$ 0.96 [range 1–5] among control subjects).

Among males, more than 2 occupations were referred by 27 RCC patients and 40 control subjects, and among females by 8 RCC patients and 4 control subjects. The median year of birth was 1926 for both males and females (ranges: female RCC patients, 1907 to 1955; female control subjects, 1911 to 1957; male RCC patients and control subjects, both 1908 to 1964).

Analysis of Job Titles and Nonprofessional Variables

Males. Table 2 reports the conditional logistic regression analysis for males. RCC was increased for BMI $>$ 25.4 (third quartile: OR, 4.91; 95% CI, 1.56–15.5; last quartile: OR, 4.42; 95% CI, 1.48–13.18) and for low-moderate alcohol intake (1 to 36 g/day). No association was found with coffee or meat intake or with use of diuretics. Phenacetin use was associated with a not significant increase in risk (OR, 1.75; 95% CI, 0.63–4.82). A significant decrease in risk was recorded for current smokers (OR, 0.32; 95% CI, 0.12–0.79).

When occupational variables were adjusted with respect to the other variables, the only significant increase in risk was found among railway workers (ie, engine drivers, traveling personnel, platform/sidings workers) (OR, 10.14; 95% CI, 1.46–70.17). As regards other occupations, the categories of managers (OR, 3.59; 95% CI, 0.82–15.59) and metal workers (OR, 2.21; 95% CI, 0.99–5.37) almost reached significance.

As can be seen from Table 4, when duration of employment was considered, Cuzik's test revealed significant trends to increased risk among managers and railway workers (*P* =

TABLE 2

Adjusted Matched OR for RCC for Some Nonprofessional and Occupational Variables in Males

Variables	Classes/(ISCO code)	Cases	Control	OR	P value	95% CI
Non professional Variables	Classes*					
BMI	≤23.4*	29 (17.4)	49 (29.3)			
	23.5–25.3	41 (24.5)	50 (29.9)	1.74	0.29	0.61–4.97
	25.4–27.6	45 (26.9)	25 (15.0)	4.91	0.00	1.56–15.50
	≥27.7	49 (29.3)	38 (22.7)	4.42	0.00	1.48–13.18
Smoking	Never smokers*	44 (26.3)	33 (19.8)			
	Current smokers	44 (26.3)	64 (38.3)	0.32	0.01	0.12–0.79
	Former smokers	78 (46.7)	69 (41.3)	0.59	0.25	0.24–1.44
Alcohol intake	0 g/day*	22 (13.2)	29 (17.4)			
	1–12 g/day	43 (25.7)	32 (19.2)	3.94	0.04	1.05–14.75
	13–24 g/day	56 (33.5)	44 (26.3)	3.37	0.03	1.10–10.34
	25–36 g/day	19 (11.4)	11 (6.6)	7.34	0.03	1.21–44.56
	37–48 g/day	9 (5.4)	22 (13.2)	0.53	0.42	0.11–2.49
	>48 g/day	16 (9.6)	27 (16.2)	1.03	0.96	0.26–4.04
Meat intake	0–4 portions/week*	89 (53.3)	85 (50.9)			
	>4 portions/week	74 (44.3)	78 (46.7)	0.80	0.53	0.40–1.59
Coffee intake	0 cups/day*	34 (20.4)	40 (23.9)			
	1–2 cups/day	87 (52.1)	78 (46.7)	0.84	0.70	0.36–1.96
	>2 cups/day	44 (26.3)	47 (28.1)	0.57	0.30	0.19–1.65
Use of diuretics		43 (25.7)	39 (23.3)	0.85	0.70	0.39–1.89
Use of phenacetin		25 (15.0)	15 (9.0)	1.75	0.27	0.63–4.82
Job titles	(ISCO code)					
Managers	(114, 12, 13)	16 (9.6)	7 (4.2)	3.59	0.08	0.82–15.59
Clerks	(233, 247, 41, 42)	25 (15.0)	35 (21.0)	1.04	0.92	0.41–2.64
Dealers	(1314, 3415, 9111)	21 (12.6)	23 (13.8)	0.64	0.39	0.23–1.76
Shop assistants	(5220)	6 (3.6)	8 (4.8)	1.16	0.86	0.21–6.42
Health care workers	(222, 223, 322, 323, 513)	4 (2.4)	3 (1.8)	2.27	0.49	0.20–2478
Police and Military personnel	(345, 5162, 010)	5 (3.0)	3 (1.8)	0.54	0.52	0.08–3.59
Motor vehicle drivers	(832)	14 (8.4)	10 (6.0)	2.12	0.34	0.45–10.00
Other white-collar workers		8 (4.8)	9 (5.4)	1.78	0.50	0.32–9.89
Production supervisors	(800)	5 (3.0)	6 (3.6)	0.30	0.25	0.03–2.33
Service workers	(5123, 915, 916)	17 (10.2)	22 (13.2)	0.47	0.17	0.16–1.39
Warehouse workers	(932, 933)	6 (3.6)	10 (6.0)	1.17	0.85	0.21–6.35
Railway workers	(831)	11 (6.6)	2 (1.2)	10.14	0.01	1.46–70.17
Food workers	(5122, 741)	8 (4.8)	7 (4.2)	0.44	0.39	0.06–2.89
Printers	(734, 8251)	7 (4.2)	5 (3.0)	1.55	0.69	0.17–13.46
Plumbers	(7136)	1 (0.6)	6 (3.6)	0.07	0.10	0.00–1.66
Painters	(7141)	5 (3.0)	9 (5.4)	0.31	0.15	0.06–1.56
Electricians	(7137, 7244, 7245)	3 (1.8)	7 (4.2)	1.44	0.81	0.06–30.60
Tailors and knitters	(7332, 743, 8263)	4 (2.4)	4 (2.4)	1.42	0.73	0.18–11.08
Shoe and leather workers	(744, 8265, 8266)	3 (1.8)	7 (4.2)	1.47	0.69	0.21–10.17
Building workers	(712, 7131, 7133, 9312, 9313)	28 (16.8)	25 (15.0)	1.18	0.73	0.43–3.25
Metal workers	(721, 722, 723, 812, 8211, 8223, 8281)	37 (22.2)	26 (15.6)	2.21	0.08	0.99–5.37
Furnace workers	(8131)	3 (1.8)	3 (1.8)	0.67	0.76	0.05–9.06
Wood workers	(7331, 742, 814)	6 (3.6)	7 (4.2)	3.24	0.19	0.55–18.90
Other blue-collar workers		17 (10.2)	23 (13.8)	0.73	0.58	0.23–2.25
Farmers	(61, 8331, 9211)	44 (26.3)	40 (23.9)	1.63	0.34	0.59–4.47

* Reference class.

OR estimated by logistic regression model based on 150 couples because of missing data.

0.04 and $P = 0.01$, respectively), but not metal workers.

Females. Table 3 reports the conditional logistic regression analysis for females. RCC was significantly associated with BMI > 25.4 (OR, 8.46; 95% CI, 1.02– 68.0). An increase in risk was also found with consumption of more than four portions of meat per week (OR, 5.27; 95% CI, 0.74– 37.1), but this did not reach significance. No significant association emerged between RCC and job titles.

Analysis of Professional Exposures

Risks associated with exposure (certain or probable) to some occupational hazards for males or females are shown in Table 5. Among the

TABLE 3
Adjusted Matched OR for RCC for Some Nonprofessional and Occupational Variables in Females

Variables	Classes/(ISCO code)	Cases	Control	OR	P value	95% CI
Non professional Variables	Classes					
BMI	≤ 25.3*	21 (40.4)	29 (55.8)			
	≥ 25.4	30 (57.7)	21 (40.4)	8.46	0.04	1.02–68.00
Smoking	Never smokers*	35 (67.3)	34 (65.4)			
	Current smokers	6 (11.5)	8 (15.4)	0.52	0.51	0.07–3.59
	Former smokers	9 (17.3)	9 (17.3)	0.34	0.28	0.05–2.41
Alcohol intake	0 g/day*	20 (38.4)	28 (53.8)			
	1–12 g/day	17 (32.7)	15 (28.8)	2.22	0.42	0.30–16.08
	> 12 g/day	15 (28.8)	9 (17.3)	4.16	0.27	0.32–53.48
Meat intake	0–4 portions/week*	22 (42.3)	33 (63.5)			
	> 4 portions/week	27 (51.9)	15 (28.8)	5.27	0.09	0.74–37.10
Coffee intake	0 cups/day*	15 (28.8)	18 (34.6)			
	1–2 cups/day	24 (46.1)	25 (48.1)	2.16	0.54	0.17–26.60
	> 2 cups/day	11 (21.1)	8 (15.4)	7.58	7.58	0.30–190.00
Use of diuretics		12 (23.1)	13 (25.0)	0.57	0.63	0.05–5.65
Use of phenacetin		9 (17.3)	9 (17.3)	1.06	0.95	0.14–7.81
Job titles	*(ISCO code)*					
Clerks	(233, 247, 41, 42)	8 (15.4)	7 (13.5)	2.19	0.63	0.08–55.00
Other white-collar workers		9 (17.3)	9 (17.3)	14.10	0.14	0.41–480.80
Housewives	(5121)	19 (36.5)	19 (36.5)	13.08	0.08	0.74–254.20
Housemaids	(913, 9141)	10 (19.2)	8 (15.4)	2.44	0.39	0.30–19.30
Tailors and knitters	(7332, 743, 263)	11 (21.1)	10 (19.2)	0.56	0.56	0.08–3.89
Other blue-collar workers		11 (21.1)	13 (25.0)	5.56	0.23	0.33–93.71
Farmers	(61, 8331, 9211)	17 (32.7)	12 (23.1)	7.07	0.14	0.50–99.60

* reference category.
OR estimated by logistic regression model, based on 43 couples, because of missing data.

TABLE 4
Job Category and Duration of Employment: Test for Trend (Cuzik's)

Duration of employment (years)	Job category					
	Managers		Railway workers		Metalworkers	
	Cases	Controls	Cases	Controls	Cases	Controls
0–1	151	160	156	165	130	141
2–10	2	1	2	0	13	10
11–20	4	4	1	1	6	4
21–30	4	2	3	0	4	3
≥ 31	6	0	5	1	14	9
P value	0.04		0.01		0.12	

categories considered for males, the only significant risk factor appeared to be exposure to asbestos (OR, 7.11; 95% CI, 1.46– 34.51). However, a not significant increase in risk was also found for exposure to welding fumes (OR, 5.67; 95% CI, 0.78–41.31). An apparent significant negative association with RCC emerged for occupational exposure to inorganic lead (OR, 0.13; 95% CI, 0.02–0.73). Among the two categories considered for females, no significant association was evident.

Extension of Matched Pairs by Substitution of Missing Data

Because of missing data, less than the total number of observations could be included into the main conditional regression analysis. To check for a possible selection bias due to the missing cases, we repeated the conditional models after substituting the missing values, first with data derived from the category with the highest level of risk, and then with data from the category with the lowest risk. We found that, apart from a general narrowing of 95% CI, the results of these models did not differ from those of the main analysis (data not shown).

Analysis with Respect to Histological Subtypes

The RCC studied were mostly of the clear-cell histological subtype. A conditional regression model applied to the male patients with this subtype (n = 141) and their matched controls

TABLE 5
Adjusted Matched OR for RCC for Some Professional Exposures

Exposures	Cases	Controls	OR	P value	95% CI
Asbestos*	11	4	7.11	0.02	1.46–34.51
Mineral oils*	11	5	1.19	0.84	0.22–6.49
Petroleum products*	16	11	2.13	0.26	0.58–7.88
Solvents*	17	22	0.79	0.61	0.31–1.98
Solvents†	3	4	1.47	0.75	0.12–17.46
Welding fumes*	8	6	5.67	0.09	0.78–41.31
Lead*	6	11	0.13	0.02	0.02–0.73
Pesticides*	12	8	1.24	0.74	0.34–4.57
Pesticides†	3	4	0.32	0.51	0.01–9.20

* Males.
† Females.
OR estimated by logistic regression models including the nonprofessional variables, based on 150 couples for males (and on 43 couples for females), because of missing data.

provided similar results to those of the main model (data not shown).

Unconditional Logistic Regression Analysis of All Respondents' Data

To gain statistical power, we also analyzed the data of all 487 respondents (249 RCC patients and 238 control subjects) using unconditional logistic regression models, for males and females, inserting the matching variables (age, admission date, place of birth, residence zone). The results showed minor variations from those of the conditional models. For males, the positive OR of phenacetin use and of managers became significant (and the negative OR of inorganic lead not significant). For females, the OR of high BMI became not significant, while that of high meat intake became significant.

To eliminate the possibility of bias induced by responses provided by next of kin, we also analyzed the data of the 366 respondents (198 RCC patients and 168 controls) who replied in person (data not shown). Among males, the OR of railway workers, asbestos exposure and high BMI remained significant. Among females, only the OR of diuretics reached borderline significance.

Discussion

Relatively little is known about occupational and other risk factors for RCC apart from their ethnic and geographical variability. Along with exposure to asbestos, employment in the metal industry and exposure to cadmium, dry-cleaning solvents or petroleum products have been identified as likely risk factors.[6] Without making any claims for completeness, epidemiological studies on individual populations in specific geographical areas may uncover previously undocumented risk factors.

The main aim of the present case−control study was to search for evidence of possible job-related risk factors for RCC. The study was conducted on a geographically and ethnically defined population, consisting almost entirely of Italians (with the exception of two non-Italian Europeans) living in the town of Bologna and its surrounding Province. Bologna is situated in central northern Italy, where there appears to be one of the highest concentrations of RCC in Europe. Various types of light industry are located in Bologna and its Province (which includes a section of the Po valley and northern Appennines), and agriculture is highly developed in the plain. Because Bologna is the principal town of the Emilia Romagna Region and the seat of an ancient University, many of its inhabitants are involved in non-industrial activities. Bologna is also a major hub in Italy's railway network.

A striking finding of the study is the significantly higher prevalence of RCC found among railway workers, even after adjusting for confounding factors, including high BMI, drinking, smoking and use of diuretics. To our knowledge, this is the third time that railway workers have been linked to a raised risk of RCC. In one of the few studies that included this occupational category, Pesch found a significant OR of about 6 for railway brakemen, signalmen and shunters.[10] Furthermore, in a study based in Montreal regarding 227 eligible cases of kidney cancer, Siemiaycki recorded an OR of 2.8 (90% CI 1.5– 5.1) among railway industry workers [11]. The workers enrolled by us all operated either on trains (as engine drivers, conductors, ticket controllers, traveling personnel, etc) or near to them (as pointsmen, platform and sidings workers, etc), while railway office personnel and construction and maintenance workers were included under other job headings (clerks, metal or construction workers, etc). Further studies are needed to exclude the possibility that the higher prevalence of RCC found by us among railway workers was not a chance finding. Nevertheless, several possible explanations could account for such an association, including exposure to asbestos or to low-frequency electromagnetic fields[12] or to diesel/coke fumes.[11,13] Although electromagnetic fields have been linked to a slightly increased risk of RCC,[14] it was not possible for us to ascertain which subgroups of workers underwent certain or very probable exposures. Use of asbestos as an insulator in wagons and locomotives is known to have caused many cases of pleural mesothelioma among railway workers both in Italy[15] and elsewhere.[13,16] Some of the railway workers studied by us had been exposed to diesel fumes or coal, and this factor may also have had some influence.

As a specific risk factor, we found that certain or very probable exposure to asbestos was associated with raised risk of RCC, with OR >7, irrespective of occupation. This finding agrees with most other studies,[6,10,17,18] with the exception of two where no significantly increased risk was found.[19,20] The link between asbestos exposure and RCC is supported by findings of asbestos fibers in the kidneys[21,22] or urine[23,24] of exposed workers. However, a recent meta-analysis[25] concluded that high asbestos exposure might entail only a slight increase in risk.

As well as railway workers, some metal workers, such as bus, truck and railway wagon builders and mechanics, tended until recently to be exposed to asbestos. In our study, metal workers showed a not significant increase in risk of RCC (with an OR of about 2 among males, becoming significant at unconditional analysis) that was not associated with duration of employment. This finding fits into a picture of conflicting data from other studies: some authors found that metal workers had a significantly higher risk of RCC,[6,11,20,26,27] while others did not.[17,19,28] The suspected increased risk in metal workers may also be attributed to exposure to a mixture of various *noxae*, including metal fumes, oils and solvents, that have been individually associated with RCC.[6] It is noteworthy that a not significant association was present in our overall study population between specific exposure to welding fumes and risk of RCC. Other studies have reported increased risk among welders.[10,18] Welding fumes can contain a variety of metals, including cadmium, exposure to which has been associated with RCC.[29] Surprisingly, in our study, exposure to inorganic lead was not associated with RCC. This unexpected finding contrasts with several other studies.[10,11,26,30,31] However, Stern and coworkers[27] also found no significant association, while a recent meta-analysis revealed only not significant evidence of a slightly increased risk.[32] At conditional regression analysis, our data actually showed a significant negative association (becoming not significant at unconditional analysis), presumably related to the fact that our controls were patients who had been admitted to hospital for other reasons, including vascular pathologies (in 4 out of 10 of the controls matched with subjects exposed to inorganic lead), and chronic lead poisoning is a likely cause of hypertension.[33]

Interestingly, managers constituted the only other job category for which some evidence of a raised risk of RCC emerged in our study (with an OR of about 3.5 among males, becoming significant only at unconditional analysis). The apparent risk was associated with extensive duration of employment. This is not the first time that this occupation has been linked to increased risk of RCC.[28] Other studies either found no association[34] or did not consider this particular professional category.[6] Some authors reported increased risk in other white-collar jobs.[26,35,36,10] A possible explanation for our finding, apart from chance, could be a sedentary lifestyle. A recent study reported that occupational physical activity is inversely associated with RCC in males[37] (although the authors were unable to provide confirmation of this[38]). Comorbids of physical inactivity, such as diabetes, obesity, hypertension and limited immune response, might be implicated. Another recent study found that risk of RCC is higher in men with raised blood pressure as well as with elevated BMI.[39]

Among the nonoccupational factors studied, high BMI has been associated with increased risk of RCC in the vast majority of studies.[30,40–48] The emergence of this particular factor (among both males and females) in the context of a hospital-based case-control study such as ours, however, may be particularly relevant. Obesity is known to determine increased morbidity in general.[49] Consequently, in a hospital one is likely to encounter a higher percentage of obese people than in the general population (standardizing for age, sex, and so on). Hence, the present study strongly underlines the relevance of high BMI as a risk factor for RCC.

By contrast, smoking showed an apparent, negative association with risk of RCC. This rather unexpected finding presumably depends on the hospital-based setting of the study, which gives rise to the so-called Berkson's bias: if some of the controls have been affected by an exposure that is also related to the disease under study, then the recorded association will be weakened (ie, biased toward the null hypothesis).[50] Extrapolating from the figures of a recent study by the Italian National Institute of Statistics[51] we can estimate that representative groups from the general population of the Emilia Romagna Region (where Bologna is the principal town), equivalent to ours for size, age and gender, would on average contain about 40 current male smokers and 4 female ones: these are remarkably close to the numbers found among our RCC patients (44 males and 6 females). Hence, if our controls had been drawn from the general population, it is unlikely that we would have found anything more than a marginally increased risk of RCC. While some positive associations have been recorded in the literature, [42,44,52–58] several studies have been unable to find any significant link between smoking habits and RCC.[20,41,59,60]

Our results suggest that if such an association does exist, it is almost certainly much weaker than what is found in most smoking-related diseases.

Use of hospital controls probably also affected our results concerning alcohol consumption, which imply an apparent increase of risk for low-moderate drinkers and no increased risk for heavy drinkers. Recent studies have demonstrated that subjects who regularly consume low-moderate quantities of wine experience lower morbidity and mortality than non-drinkers or heavy drinkers.[61] This factor could explain our data (as well as the results of others[44,52] who hypothesized that high alcohol intake might be protective).

In addition to the effects of Berkson's bias due to the hospital-based setting of the study,[50] other reasons for caution when interpreting our data include the use of multiple comparisons, which could give rise to occasional chance associations. However, it should be noted that Cuzik's test for trend indicated that increased risk of RCC among railway workers correlated with duration of employment. Furthermore, causative exposures (eg, to asbestos) could provide a rational explanation for this finding. Although the study population was relatively small, (324 matched pairs) the percentage of responders (75% subjects, 67% matched pairs) seem acceptable. It seems unlikely that responses provided by next of kin (for 24% of subjects) affected reliability since exclusion of these data left the main study findings unchanged. The fact that lifetime employment in more than two professions was reported more often by control subjects ($n = 40$) than by RCC patients ($n = 27$) seems to exclude the possibility that our results were affected by lack of information provided by controls. Although overmatching of professions can limit the finding of true associations when cases and controls are residentially matched, it should be noted that the Province of Bologna contains a wide variety of small-medium sized industry, agriculture and service-sector employment. Conversely, the high number of railway workers employed around Bologna—a railway hub playing a similar role to that of Crewe in Britain or Lyon in France—may have helped uncover an association with RCC that could be more difficult to reveal in other populations.

In conclusion, this hospital-based case–control study on a geographically defined population suggests that railway workers operating either on or near to trains could have increased risk of developing RCC. The role of asbestos exposure as a likely specific risk factor—as evidenced in the present study—provides a possible explanation for this finding. Other concomitant factors could include exposure to electromagnetic fields and diesel or coke fumes. Our data suggest that metal workers could also be at increased risk of RCC. Future cohort studies should help clarify the possible risks encountered by railway workers, metal workers, and maybe also by managers. In our study, managers showed a slight increase in risk of RCC, perhaps due to a more sedentary lifestyle. The weight of evidence that high BMI is a risk factor for RCC provides another argument for preventing obesity.

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References

1. Wunderlich H, Schumann S, Jantitzky V, et al. Increase of renal cell carcinoma incidence in central Europe. *Eur Urol.* 1998;33:538–541.
2. Chow WH, Devesa SS, Warren JL, Fraumeni JF Jr. Rising incidence of renal cell cancer in the United States. *JAMA.* 1999; 281:1628–1631.
3. Tavani A, La Vecchia C. Epidemiology of renal cell carcinoma. *J Nephrol.* 1997; 10:93–106.
4. Parkin DM, Whelan SL, Ferlay J, et al. *Cancer Incidence in Five Continents* (Vol 7). Lyon, France, International Agency for Research on Cancer (IARC) Scientific Publications No. 143, 1997; p. 1240.
5. McLaughlin JK, Lipworth L. Epidemiologic aspects of renal cell cancer. *Semin Oncol.* 2000;27:115–123.
6. Mandel JS, McLaughlin JK, Schlehofer B, et al. International renal cell cancer study. IV. Occupation. *Int J Cancer.* 1995;61:601–605.
7. International Labour Organization. *International Standard Classification of Occupations.* Geneva: ILO, 1988.
8. Breslow NE, Day NE. *Statistical Methods in Cancer Research.* Vol. 1. Lyon, International Agency for Research on Cancer, 1980.
9. Cuzick J A. Wilcoxon-type test for trend. *Stat Med.* 1985;4:87–90.
10. Pesch B, Haerting J, Ranft U, et al. Occupational risk factors for renal cell carcinoma: agent-specific results from a case-control study in Germany. *Int J Epidemiol.* 2000;29:1014–1024.
11. Siemiatycki J. *Risk Factors for Cancer in Workplace.* Boca Raton, FL: CRC Press, 1991.
12. Floderus B, Tornqvist S, Stenlund C. Incidence of selected cancer in Swedish railway workers, 1961–1979. *Cancer Causes Control.* 1994;5:189–194.
13. Nokso-Koivisto P, Pukkala E. Past exposure to asbestos and combustion products and incidence of cancer among Finnish locomotive drivers. *Occup Environ Med.* 1994;51:330–334.
14. Floderus B, Stenlund C, Persson T. Occupational magnetic field exposure and site-specific cancer incidence: a Swedish cohort study. *Cancer Causes Control.* 1999;10:323–332.
15. Maltoni C, Pinto C, Carnuccio R, et al. Mesotheliomas following exposure to asbestos used in railroads: 130 Italian cases. *Med Lav.* 1995;86:461–477.
16. Mancuso TF. Relative risk of mesothelioma among railroad machinists exposed to chrysotile. *Am J Ind Med.* 1988;15: 483–486.
17. McCredie M, Stewart JH. Risk factors for kidney cancer in New South Wales. IV. Occupation. *Br J Ind Med.* 1993;50:349–354.
18. Puntoni R, Russo L, Zannini D, et al. Mortality among dock-yard workers in Genoa, Italy. *Tumori.* 1977;63:91–96.
19. Mellemgaard A, Engholm G, McLaughlin JK, Olsen JH. Occupational risk fac-

tors for renal cell carcinoma in Denmark. *Scand J Environ Med.* 1994;20:160–165.
20. Schlehofer B, Heuer C, Blettner M, et al. Occupation, smoking and demographic factors, and renal cell carcinoma in Germany. *Int J Epidemiol.* 1995;24:51–57.
21. Huang J, Hisanaga N, Sakai K, et al. Asbestos fibers in human pulmonary and extrapulmonary tissues. *Am J Ind Med.* 1988;14:331–339.
22. Pollice L, Molinini R, Paoletti L, et al. Asbestos fiber count in extra-pulmonary tissues. *G Ital Med Lav Erg.* 1997;19:39–41.
23. Finn MB, Hallenbeck WH. Detection of chrysotile in workers' urine. *Am Ind Hyg Assoc J.* 1985;46:162–169.
24. Guillemin MP, Litzistorf G, Buffat PA. Urinary fibers in occupational exposure to asbestos. *Ann Occup Hyg.* 1989;33:219–233.
25. Sali D, Boffetta P. Kidney cancer and occupational exposure to asbestos: a meta-analysis of occupational cohort studies. *Cancer Causes Control.* 2000;11:37–47.
26. Partanen T, Heikkila P, Hernberg S, et al. Renal cell cancer and occupational exposure to chemical agents. *Scand J Work Environ Health.* 1991;17:231–239.
27. Stern FB, Sweeney MH, Ward E. Proportionate mortality among unionized construction ironworkers. *Am J Ind Med.* 1997;31:176–187.
28. Aupèrin A, Benhamou S, Ory-Paoletti C, Flamant R. Occupational risk factors for renal cell carcinoma: a case-control study. *Occup Environ Med.* 1994;51:426–428.
29. Kolonel LN. Association of cadmium with renal cancer. *Cancer.* 1976;37:1782–1787.
30. Landrigan PJ, Goyer RA, Clarkson TW, et al. The work-relatedness of renal disease. *Arch Environ Health.* 1984;39:225–230.
31. Moore MR, Meredith PA. The carcinogenicity of Lead. *Arch Toxicol.* 1979;42:87–94.
32. Steenland K, Boffetta P. Lead and cancer in humans: where are we now? *Am J Ind Med.* 2000;38:295–299.
33. Batuman V. Lead nephropathy, gout, and hypertension. *Am J Med Sci.* 1993;305:241–247.
34. Delahunt B, Bethwaite PB, Nacey JN. Occupational risk for renal cell carcinoma. A case-control study based on the New Zealand cancer registry. *Br J Urol.* 1995;75:578–582.
35. Lowery JT, Peters JM, Deapen D, London SJ. Renal cell carcinoma among architects. *Am J Ind Med.* 1991;20:123–125.
36. McLaughlin JK, Malker HSR, Stone BJ, et al. Occupational risk for renal cancer in Sweden. *Br J Ind Med.* 1987;41:119–123.
37. Bergstrom A, Moradi T, Lindblad P, et al. Occupational physical activity and renal cell cancer: a nationwide cohort study in Sweden. *Int J Cancer.* 1999;83:186–191.
38. Bergstrom A, Terry P, Lindblad P, et al. Physical activity and risk of renal cell cancer. *Int J Cancer.* 2001;92:155–157.
39. Chow WH, Gridey G, Fraumeni JF Jr., Jarvholm B. Obesity, hypertension and the risk of kidney cancer in men. *N Engl J Med.* 2000;343:1305–1311.
40. Asal NR, Geyer JR, Risser DR, et al. Risk factors in renal cell carcinoma. II. Medical history, occupation, multivariate analysis, and conclusions. *Cancer Detect Prev.* 1988;13:263–279.
41. Goodman MT, Morgenstern H, Wynder EL. A case-control study of factors affecting the development of renal cell cancer. *Am J Epidemiol.* 1986;124:926–941.
42. Kreiger N, Marrett LD, Dodds L, et al. Risk factors for renal cell carcinoma: results of a population-based case-control study. *Cancer Causes Control.* 1993;4:101–110.
43. Lindblad P, Wolk A, Bergstrom R, et al. The role of obesity and weight fluctuations in the etiology of renal cell cancer: a population-based case-control study. *Cancer Epidemiol Biomarkers Prev.* 1994;3:631–639.
44. McLaughlin JK, Gao YT, Gao RN, et al. Risk factors for renal cell cancer in Shanghai, China. *Int J Cancer.* 1992;52:562–565.
45. Mellemgaard A, Lindblad P, Schlehofer B, et al. International renal cell cancer study. III. Role of weight, height, physical activity, and use of amphetamines. *Int J Cancer.* 1995;60:350–354.
46. Shapiro JA, Williams MA, Weiss NS. Body mass index and risk of renal cell carcinoma. *Epidemiology.* 1999;10:188–191.
47. Yu MC, Mack TM, Hanisch R, et al. Cigarette smoking, obesity, diuretic use, and coffee consumption as risk factors for renal cell carcinoma. *J Natl Cancer Inst.* 1986;77:351–356.
48. Bergstrom A, Hsieh CC, Lindblad P, et al. Obesity and renal cell cancer- a quantitative review. *Br J Cancer.* 2001;85:984–990.
49. Kopelman PG. Obesity as a medical problem. *Nature.* 2000;404:635–643.
50. Feinstein AR, Walter SD, Horwitz RI. An analysis of Berkson's bias in case-control studies. *J Chronic Dis.* 1986;397:495–504.
51. Servizio Relazioni con il Pubblico e Statistica qqdella Regioneemilia Romagna: *La vita quotidiana in Emilia-Romagna. Risultati dell'indagine multiscopio sulle famiglie del* 1996, edited by Franco Angeli, Milan, Italy, 1998, 130–133.
52. Benichou J, Chow WH, McLaughlin JK, et al. Population attributable risk of renal cell cancer in Minnesota. *Am J Epidemiol.* 1998;148:424–430.
53. McLaughlin JK, Mandel JS, Blot WJ, et al. A population-based case-control study of renal cell carcinoma. *J Natl Cancer Inst.* 1984;72:275–284.
54. McLaughlin JK, Lindblad P, Mellemgaard A, et al. International renal cell cancer study. I. Tobacco use. *Int J Cancer.* 1995;60:194–198.
55. Band PR, Spinelli JJ, Threlfall WJ, et al. Identification of occupational cancer risk in British Columbia. *J Occup Environ Med.* 1999;41:224–232.
56. Brownson RC. A case-control study of renal cell carcinoma in relation to occupation, smoking, and alcohol consumption. *Arch Environ Health.* 1988;43:238–241.
57. Benhamou S, Lenfant MH, Ory-Paoletti C, Flamant R. Risk factors for renal cell carcinoma in a French case-control study. *Int J Cancer.* 1993;55:32–36.
58. Chin BC, Lynch CF, Cerhan JR, Cantor KP. Cigarette smoking and risk of bladder, pancreas, kidney and colorectal cancer in Iowa. *Ann Epidemiol.* 2001;11:28–37.
59. Augustsson K, Skog K, Jagerstad M, et al. Dietary heterocyclic amines and cancer of colon, rectum, bladder, and kidney: a population-based study. *Lancet.* 1999;353:703–707.
60. Talamini R, Baròn AE, Barra S, et al. A case-control study of factor for renal cell cancer in northern Italy. *Cancer Causes Control.* 1990;1:125–131.
61. Farchi G, Fidanza F, Giampaoli S, et al. Alcohol and survival in the Italian rural cohorts of Seven Countries Study. *Int J Epidemiol.* 2000;29:667–671.