Exhibit 274

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INTERNATIONAL RENAL-CELL CANCER STUDY. IV. OCCUPATION

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The relationship between renal-cell cancer (RCC) and occupation was investigated in an international multicenter population-based case-control study. Study centers in Australia, Denmark, Germany, Sweden and the United States interviewed 1732 incident RCC cases and 2309 controls. Significant associations were found with employment in the blast-furnace or the coke-oven industry [relative risk (RR), 1.7; 95% confidence interval (CI), 1.1–2.7], the iron and steel industry (RR, 1.6; 95% CI, 1.2–2.2) and exposure to asbestos (RR, 1.4; 95% CI, 1.1–1.8), cadmium (RR, 2.0; 95% CI, 1.0–3.9), dry-cleaning solvents (RR, 1.4; 95% CI, 1.1–1.7), gasoline (RR, 1.6; 95% CI, 1.2–2.0) and other petroleum products (RR, 1.6; 95% CI, 1.3–2.1). Asbestos, petroleum products and dry-cleaning solvents appear to merit further investigation, in view of the relationship between risk and duration of employment or exposure and after adjustment for confounding. There was a negative association between RCC and education, but it was not consistent across all centers. Overall, the results of our multicenter case-control study suggest that occupation may be more important in the etiology of RCC than indicated by earlier studies.

Renal-cell cancer (RCC) is generally not considered an occupation-associated cancer, although a number of studies have reported an association with asbestos (Selikoff *et al.*, 1979; Enterline *et al.*, 1987; Maclure, 1987; Smith *et al.*, 1989). Associations have also been reported with coke-oven work (Redmond *et al.*, 1981), dry cleaning and laundry (Blair *et al.*, 1979; Brown and Kaplan, 1987), cadmium (Kolonel, 1976) and gasoline (Partanen, 1991). However, except for asbestos, no occupational exposure or occupation has been consistently linked to RCC.

Our multicenter international case-control study of RCC provided an opportunity to further evaluate the etiologic role of occupation. In addition, we evaluated the relation between RCC and education as a measure of socio-economic status.

MATERIAL AND METHODS

Details of the methods are presented elsewhere (McLaughlin *et al.*, 1995). Briefly, we carried out our multicenter collaborative case-control study in order to evaluate factors possibly related etiologically to RCC. There were 6 study centers in 5 countries: Australia (study area referred to as Sydney), Denmark (Denmark), Germany (Berlin and Heidelberg), Sweden (Uppsala) and the USA (Minnesota). Although each center was independently funded, and had different starting dates, there was a common study protocol, and the instruments for data collection were similar.

Cases were incident renal-cell adenocarcinomas (ICD-9 189.0) from 6 geographic regions, among men and women aged 20 to 79 (20 to 75 in Heidelberg) who were diagnosed between 1989 and 1991 and confirmed by histopathology or cytology. In all centers except Sydney and Minnesota, only individuals born in the country concerned were included. Population-based cancer registries were the main source of cases in all centers except Berlin and Heidelberg, where cases were ascertained through an active surveillance system of all clinical and pathological departments in which renal-cell cancer was diagnosed or treated. Controls, frequency-matched to cases by gender and 5-year age groups, were selected from registers covering the entire population (Denmark, Uppsala), electoral rolls (Sydney), residential lists (Berlin, Heidelberg) or Health Care Financing Administration lists (Minnesota; controls aged 65 to 79 years). Random-digit dialing was used to select controls aged 20 to 64 in Minnesota. Information was collected at face-to-face interviews by specially trained interviewers. With the exception of the 2 German centers, where cases were interviewed in the hospital, most participants were interviewed in their homes. Information was sought on use of tobacco, diuretics, analgesics, anti-hypertensive drugs, diet pills, hormones and alcohol, height and weight, physical activity, medical and reproductive histories, family history of cancer, occupation and demographic characteristics. Four of the centers (Sydney, Denmark, Uppsala and Minnesota) inquired about specific occupations, industries and exposures of prime interest, while the 2 centers in Germany (Berlin and Heidelberg) collected complete occupational histories. Occupations and industries were coded by all centers according to standard occupational and industrial classification schemes (International Labour Office, 1968, 1988; UN Department of Economic and Social Affairs, 1968, 1971, 1990; US Department of Commerce, 1980; US Office of Management and Budget, 1987).

As expected, there were differences among centers in the specific occupations, industries and exposures available for analysis. Only those common to all centers were included in our analysis. Exposures were ascertained in a similar manner in all centers.

Analyses included descriptive statistics with number and percent of respondents ever/never worked or exposed and number of years worked or exposed for each of the occupations, industries and exposures. Analyses were conducted separately by gender. Number of years worked or exposed were dichotomized or stratified into tertiles depending upon the number of available respondents. The cutpoints were derived from the distributions of values among male and female controls.

The association between occupation and risk of RCC was measured using the odds ratio (OR), which is an estimation of the relative risk (RR). Subjects were considered exposed if they worked for at least one year in the specific occupation or reported exposure to the principal agents for one year or longer. Logistic regressions were derived for ever/never worked or exposed, for men and women separately, and for number of

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TABLE I – DISTRIBUTION OF SELECTED CHARACTERISTICS AMONG CASES AND CONTROLS IN THE INTERNATIONAL RENAL-CELL-CANCER STUDY

Characteristic	Number (%)[1] Cases	Number (%)[1] Controls
Study center		
Australia	250 (14)	248 (11)
Berlin	205 (12)	354 (15)
Denmark	365 (21)	394 (17)
Heidelberg	255 (15)	280 (12)
Sweden	377 (22)	350 (15)
USA	280 (16)	683 (30)
Gender		
Male	1050 (61)	1429 (62)
Female	682 (39)	880 (38)
Age at diagnosis or interview (in years)		
< 58	571 (33)	752 (33)
58–68	620 (36)	794 (34)
> 68	541 (31)	763 (33)
Smoking		
No use	585 (35)	846 (38)
Ever smoked		
Current smoker	538 (32)	592 (27)
Former smoker	545 (33)	762 (35)
BMI (usual weight)		
< 23.1	363 (21)	575 (25)
23.1–24.7	376 (22)	579 (25)
24.8–26.5	447 (26)	580 (25)
≥ 26.6	546 (32)	575 (25)

[1]Percentages may not add to 100, due to rounding.

years worked or exposed for those RR that were statistically significant ($p \leq .05$) or near-significant on the dichotomized analyses. The analyses were adjusted for age, center, body-mass index (BMI) and cigarettes smoked before 1987, which was divided into pack-year quartiles based on the separate distribution of male and female controls. Differences across centers were evaluated using heterogeneity tests. Because of an inverse association between education and RCC in 3 of the 6 centers, further adjustment for education was performed for the occupational results, with virtually no difference for education-adjusted RR. The results reported here are therefore unadjusted for education.

RESULTS

There were 1732 cases and 2309 controls (Table I). Approximately 60% were male, 14% were under age 50, and about 62% were over age 60 at the time of diagnosis or interview. Overall response rates were 72.3% for cases and 74.7% for controls.

The distribution of industries, occupations and exposures for cases and controls by gender is presented in Table II. Less than 10% of women reported that they worked in any of the industries or occupations or were exposed to any of the agents of interest. Exposure to dry-cleaning solvents was reported by 8.4% of the female cases and 4.8% of the female controls. A larger proportion of men reported employment or exposures of interest, particularly ever having worked in the iron and steel industry (10.8% of cases and 6.1% of controls), ever employed as shopfloor workers (*i.e.,* machinist, tool worker and similar jobs) (14.2 and 11.4%) and ever exposed to

TABLE II – DISTRIBUTION OF INDUSTRIES, OCCUPATIONS AND EXPOSURES IN CASES AND CONTROLS BY GENDER, ALL CENTERS

	Men				Women				Men and women			
	Cases		Controls		Cases		Controls		Cases		Controls	
	N	%[1]	N	%[1]	N	%[1]	N	%[1]	N	%[1]	N	%[1]
Industry												
Oil refinery	21	2.0	20	1.4	3	0.4	2	0.2	24	1.4	22	1.0
Blast furnaces and coke ovens	57	5.4	40	2.8	4	0.6	1	0.1	61	3.5	41	1.8
Iron and steel	113	10.8	87	6.1	10	1.5	8	0.9	123	7.1	95	4.1
Dry cleaning	8	0.8	12	0.8	15	2.2	16	1.8	23	1.3	28	1.2
Printing or graphics	39	3.7	41	2.9	23	3.4	25	2.9	62	3.6	66	2.9
Military	290	31.8	445	37.4	8	1.3	10	1.3	298	19.6	455	23.3
Occupation												
Shop floor worker[2]	149	14.2	163	11.4	12	1.8	19	2.2	161	9.3	182	7.9
Welder	77	7.3	85	6.0	4	0.6	6	0.7	81	4.7	91	3.9
Dentist	1	0.1	3	0.2	3	0.4	2	0.2	4	0.2	5	0.2
Physician	9	0.9	13	0.9	0	0.0	4	0.5	9	0.5	17	0.7
Gas-station attendant	56	6.4	73	5.9	4	0.7	14	1.8	60	4.1	87	4.3
Exposures												
Asbestos	200	19.1	187	13.1	6	0.9	10	1.1	206	11.9	197	8.6
Dry-cleaning solvents	245	23.4	223	15.6	57	8.4	42	4.8	302	17.5	265	11.5
Gasoline	164	18.7	189	15.2	16	2.7	18	2.3	180	12.2	207	10.2
Cutting oils or mists	168	16.0	191	13.4	10	1.5	14	1.6	178	10.3	205	8.9
Other petroleum products[3]	195	18.6	187	13.1	7	1.0	11	1.3	202	11.7	198	8.6
Radiation or radioactive materials	18	1.7	33	2.3	12	1.8	17	1.9	30	1.7	50	2.2
Cadmium	25	2.4	15	1.1	3	0.4	3	0.3	28	1.6	18	0.8
Insecticides, herbicides, pesticides	98	9.4	151	10.6	22	3.2	21	2.4	120	6.9	172	7.5

[1]Percent of subjects who responded "yes" to ever worked in industry or occupation or ever exposed.–[2]Includes occupations such as machinist, tool worker.–[3]Other petroleum products includes jet fuel, heating oil, kerosene or diesel fuel.

TABLE III – RELATIVE RISK (RR) AND 95% CONFIDENCE INTERVAL (CI) FOR INDUSTRIES, OCCUPATIONS AND OCCUPATIONAL EXPOSURES (MEN ONLY)

Industry/Occupation	Cases[1]	Controls[2]	RR[3]	95% CI
Industry				
Blast furnace and coke ovens	57	40	1.7	1.1–2.7
Dry-cleaning industry	8	12	0.9	0.3–2.4
Iron or steel industry	113	87	1.6	1.2–2.2
Military	290	445	1.0	0.8–1.3
Oil refinery	21	20	1.3	0.6–2.4
Printing or graphics industry	39	41	1.3	0.8–2.0
Occupation				
Dentist	1	3	0.5	0.0–5.3
Physician	9	13	1.0	0.4–2.5
Shop floor worker	149	163	1.1	0.8–1.4
Welder	77	85	1.1	0.8–1.6
Gas-station attendant	56	73	1.3	0.9–1.9
Exposure				
Asbestos	200	187	1.4	1.1–1.8
Cadmium	25	15	2.0	1.0–3.9
Cutting oils or mists	168	191	1.2	0.4–1.5
Dry-cleaning solvents	245	223	1.4	1.1–1.7
Gasoline	164	189	1.6	1.2–2.0
Other petroleum products[4]	195	187	1.6	1.3–2.1
Pesticides	98	151	1.2	0.9–1.5
Radiation or radioactive materials	18	33	0.7	0.4–1.3

[1]Number of exposed cases.–[2]Number of exposed controls.–[3]RR from logistic regression analysis, adjusted for age, smoking status, body-mass index, education and study center.–[4]Includes jet fuels, heating oils, kerosene, diesel fuel.

asbestos (19.1 and 13.1%), dry-cleaning solvents (23.4 and 15.6%), gasoline (18.7 and 15.2%), cutting oils or mists (16.0 and 13.4%), other petroleum products (*e.g.,* jet fuel, heating oil, kerosene and diesel fuel) (18.6 and 13.1%).

As shown in Table III, significant associations for men were found for the blast furnace (RR, 1.7; 95% CI, 1.1–2.7) and iron and steel industries (RR, 1.6; 95% CI, 1.2–2.2) and for the following exposures: asbestos (RR, 1.4; 95% CI, 1.1–1.8), cadmium (RR, 2.0; 95% CI, 1.0–3.9), dry-cleaning solvents (RR, 1.4; 95% CI, 1.1–1.7), gasoline (RR, 1.6; 95% CI, 1.2–2.0) and other petroleum products (RR, 1.6; 95% CI, 1.3–2.1). The finding for having worked in a gasoline station was elevated but not statistically significant (RR, 1.3; 95% CI, 0.9–1.9).

Among women, the only association that was statistically significant was with dry-cleaning solvents (RR, 1.6; 95% CI, 1.0 to 2.7).

There was no clear pattern of increasing risks with increasing duration of employment except for other petroleum products, which showed an increasing risk with duration (Table IV). Adjusting for exposure to gasoline did not materially alter the risks (from 1.5, 1.6 and 1.9 to 1.6, 1.9 and 1.8, respectively, for the 3 exposure categories). There was no significant trend for duration of gasoline exposure. Adjusting gasoline for other petroleum products reduced the risks from 1.6, 1.4 and 1.6 to 1.5, 1.1 and 1.2, respectively, for the 3 categories of duration of gasoline exposure.

Employment in the blast-furnace and iron and steel industries and exposure to cadmium were negatively associated with duration. This was particularly striking for exposure to cadmium, where RR declined from 4.3 for 1 to 10 years of exposure to 1.0 for 31 to 41 years of exposure.

Fifty-six percent of cases and 48% of controls had less than a high-school education. More controls than cases had some college education. Table V shows the relationship with education. There was a significantly negative association between renal-cell cancer and education, restricted mainly to individuals with college or university education. Both men and women

TABLE IV – RELATIVE RISKS (RR) AND 95% CONFIDENCE INTERVALS (CI) FOR INDUSTRIES, OCCUPATIONS AND OCCUPATIONAL EXPOSURES (MEN ONLY)

Duration (in years) of occupation exposure	Cases[1]	Controls[2]	RR[3]	95% CI
Blast furnace				
1–2	21	12	1.9	0.9–4.0
3–7	18	13	1.6	0.7–3.3
8–41	14	13	1.6	0.7–3.4
Iron or steel industry				
1–3	37	26	2.1	1.2–3.6
4–21	38	32	1.4	0.8–2.2
22–59	37	28	1.5	0.9–2.6
Asbestos				
1–8	72	63	1.5	1.0–2.1
9–24	67	60	1.5	1.0–2.1
25–57	58	63	1.2	0.8–1.8
Cadmium				
1–11	16	5	4.3	1.5–12.2
12–30	5	5	1.0	0.3–3.6
31–44	4	5	1.0	0.3–3.7
Dry-cleaning solvents				
1–7	70	75	1.2	0.9–1.8
8–25	98	71	1.7	1.2–2.4
26–60	75	76	1.2	0.9–1.8
Gasoline				
1–5	56	63	1.6	1.1–2.4
6–27	56	62	1.4	0.9–2.1
28–62	52	63	1.6	1.1–2.5
Other petroleum products				
1–9	49	56	1.5	1.0–2.2
10–24	75	66	1.6	1.1–2.3
25–60	71	62	1.9	1.8–2.7

[1]Number of exposed cases.–[2]Number of exposed controls.–[3]Relative risk from logistic regression analysis, adjusted for age, smoking status, body-mass index, education and study center.

TABLE V – RELATIVE RISKS (RR) AND 95% CONFIDENCE INTERVALS (CI) FOR EDUCATION, BY GENDER

	Cases	Controls	RR	95% CI
	Men[1]			
Less than high school	556	653	1.0	
High school, technical school	326	426	0.9	0.8–1.2
College or university	165	350	0.7	0.6–0.9
	Women[1]			
Less than high school	404	454	1.0	
High school, technical school	201	282	1.0	0.7–1.2
College or university	70	142	0.7	0.5–1.0
	Totals[2]			
Less than high school	960	1107	1.0	
High school, technical school	527	708	1.0	0.8–1.1
College or university	235	492	0.7	0.6–0.9

[1]Adjusted for age, smoking, BMI and hypertension, center.–[2]Adjusted for age, gender, smoking, BMI and hypertension, center.

with this level of education had a 30% reduction in risk. However, the findings were not consistent across all study centers. There was no association with education in Sydney, Uppsala and Minnesota, although heterogeneity tests across centers did not reveal statistically significant differences.

DISCUSSION

This is the largest case-control study of renal-cell cancer to date, involving 6 centers from 5 countries. Each of the centers used a shared study protocol and, where feasible, adopted common procedures. The occupational information was collected in 2 ways. The 2 centers in Germany ascertained detailed occupational histories and then coded according to standardized classifications. The other 4 centers asked about specific occupations and exposures, though the lists varied somewhat among the centers, depending on local occupations and particular interests. The data presented in this report represent only those occupations and exposures common to all centers. Individual center reports will be presented elsewhere.

Generally, population-based case-control studies are not the most accurate or efficient study method for ascertaining specific occupational risks, because of reliance on recall and the great diversity of jobs in a particular population, particularly among those in the non-professional classes. Cohort studies of workers in a specific occupation or exposed to a specific agent is a better approach, particularly when exposure data are available or can be derived from work histories.

Despite the limitations, this study confirmed a number of reported associations, including those for employment in the blast-furnace or coke-oven and iron and steel industries, and for exposure to asbestos, cadmium, dry-cleaning solvents, and to other petroleum products.

Two industries, blast furnaces and iron and steel, were significantly associated with renal-cell cancer. A large study of the iron and steel industry in the United States found an increased risk of kidney cancer among workers, particularly among those exposed to the coke ovens (Redmond *et al.*, 1981). Although, as with those workers, we found no increasing risk with duration of employment. Moreover, a 30-year follow-up of these coke-oven workers has found no significantly increased risk for renal-cell cancer (Costantino *et al.*, 1995).

Several investigators have found increased risks of kidney cancer associated with exposure to asbestos (Selikoff *et al.*, 1979; Enterline *et al.*, 1987; Maclure, 1987; Smith *et al.*, 1989). Experimental evidence lends support to a causal link. Asbestos fibers have been found in the kidneys of individuals with high exposures (Huang *et al.*, 1988) and in the kidneys of exposed animals (Kanazawa *et al.*, 1970). Finn and Hallenbeck (1985) found more asbestos fibers in the urine of asbestos workers than in non-exposed controls. Case-control studies not showing an association with asbestos exposure had small numbers of exposed workers (McLaughlin *et al.*, 1984; Yu *et al.*, 1986; Asal *et al.*, 1988; Brownson, 1988; Partanen *et al.*, 1991; McLaughlin *et al.*, 1992). Our study, with 200 exposed cases, provides additional evidence that asbestos increases the risk of kidney cancer. Nevertheless, further research of asbestos-exposed workers is needed to demonstrate a relationship with either duration of employment or amount of exposure before a causal association can be confidently concluded.

Cadmium can affect the kidney (Doll, 1992). Cadmium is also known to affect DNA (Snow, 1992). Cadmium exposure, estimated from cigarettes, food and work histories was associated with kidney cancer in a hospital-based case-control study (Kolonel, 1976). However, several other case-control and cohort studies of cadmium-exposed workers have reported no association with cadmium (McLaughlin *et al.*, 1984; Armstrong and Kazantzis, 1985; Thun *et al.*, 1985; Yu *et al.*, 1986; Asal *et al.*, 1988; Brownson, 1988). We found a significant association with exposure to cadmium, but an inverse dose-response effect. Our findings, along with those from prior studies, would argue against a causal interpretation.

Previous studies have reported excess risks among laundry and dry-cleaning workers (Blair *et al.*, 1979; Asal *et al.*, 1988; Brown and Kaplan, 1987). However, a large retrospective cohort mortality study of these workers found no increased risk from kidney cancer (Blair *et al.*, 1990). We found a significant association with dry-cleaning solvents both for men and for women, although risk by duration of exposure was inconsistent. Because we observed the association in both sexes, further research on these solvents should be pursued.

McFarland *et al.* (1984) reported a high rate of renal cancer in male rats exposed long-term to fumes from unleaded gasoline. However, further research suggested that the effect in rats was due to protein-droplet nephropathy resulting from a chemically induced cytoxic response to gasoline, which frequently results in development of a renal neoplasm (Hard *et al.*, 1993). The protein, an alpha 2 micro-globulin, unique to certain strains of male rats, does not have an exact human analogue. The initial finding by McFarland *et al.* (1984) stimulated investigation of the relation with gasoline. McLaughlin *et al.* (1985) found a slight upward trend in risk with length of employment. A case-control study in Finland showed a significant association with gasoline exposure and a dose-response relationship with level but not with duration of exposure (Partanen *et al.*, 1991). Other case-control and cohort studies of exposed workers, however, have found no association with gasoline (Yu *et al.*, 1986; McLaughlin *et al.*, 1992; McLaughlin, 1993). We found a significant association with gasoline exposure, but no dose-response effect. However, adjusting for other petroleum products reduced the magnitude of the association. It appears that the weight of the epidemiologic evidence does not support a relationship between gasoline and risk of renal-cell cancer.

A case-control study of exposure to petroleum-derived liquids found a significant association between kidney cancer and jet fuel (Siemiatycki *et al.*, 1987). A study of aviation maintenance workers exposed to a variety of chemicals, including jet fuel, found no excess risk (Spirtas *et al.*, 1991). Exposure to hydrocarbons has also been linked to renal-cell cancer in 2 small case-control studies (Kadamani *et al.*, 1981; Sharpe *et al.*, 1989). We found a significant association with other petroleum products and a dose-response relationship, which was not confounded by exposure to gasoline. Other petroleum products included jet fuel, heating oil, and kerosene or diesel fuel. We were unable to distinguish among these products, since they were inquired about as a group. However, our observation may provide the basis for future individual examinations of these fuels.

Record-linkage studies in Sweden and Denmark found a significantly elevated risk of renal-cell cancer for health-care workers, including physicians and dentists (McLaughlin *et al.*, 1987; Lynge and Thygesen, 1990). This finding was not confirmed in our study. In view of the large number of comparisons in the earlier Swedish and Danish studies, chance may account for the result. On the other hand, there were relatively few physicians and dentists in our case-control study.

Education was negatively associated with renal-cell cancer. This finding was unexpected, as previous case-control studies found no association (McLaughlin *et al.*, 1984; Kreiger *et al.*, 1993). One exception was a study in Oklahoma which showed an inverse trend with education (Asal *et al.*, 1988). The lack of consistency across centers in our study suggests caution when interpreting this finding. Adjustment for education had no material effect on the RR associated with occupation or exposure.

In summary, although renal-cell cancer is not usually linked with occupation, we observed a number of associations, most of them consistent with previous reports. Our finding for asbestos supports a number of earlier studies and suggests a relation with renal-cell cancer. The other occupational associations we observed lack the consistency in the literature of the asbestos finding. But the risk for exposure to other petroleum products, such as jet fuel, heating oil, kerosene and diesel fuel, warrants further investigation. Our observation on exposure to dry-cleaning solvents parallels some earlier studies, but we found little effect of duration, although this may reflect the nature of population-based case-control studies of occupation. The results of this pooled analysis indicate that occupation may play a larger role in the etiology of renal-cell cancer than previously thought.

REFERENCES

ARMSTRONG, B.G. and KAZANTZIS, G., Prostatic cancer and chronic respiratory and renal disease in British cadmium workers: a case-control study. *Brit. J. ind. Med.*, **42,** 540–545 (1985).

ASAL, N.R., LEE, E.T., GREGOR, J.R., KADAMANI, S., RISSER, D.R. and CHERNG, N., Risk factors in renal-cell carcinoma. II. Medical history, occupation. Multivariate analysis and conclusions. *Cancer Det. Prev.*, **13,** 263–279 (1988).

BLAIR, A., DECOUFLE, P. and GRAUMAN, D., Causes of death among laundry and dry-cleaning workers. *Amer. J. public Health,* **69,** 508–511 (1979).

BLAIR, A., STEWART, P.A., TOLBERT, P.E., GRAUMAN, D., MORAN, F.X., VAUGHT, J. and RAYNER, J., Cancer and other causes of death among a cohort of dry cleaners. *Brit. J. ind. Med.*, **47,** 162–168 (1990).

BROWN, D.P. and KAPLAN, S.D., Retrospective cohort mortality study of dry-cleaner workers using perchloroethylene. *J. occup. Med.*, **29,** 535–541 (1987).

BROWNSON, R.C., A case-control study of renal-cell carcinoma in relation to occupation, smoking and alcohol consumption. *Arch. environ. Health,* **43,** 238–241 (1988).

COSTANTINO, J.P., REDMOND, C.K. and BEARDEN, A., Occupational related cancer risk among coke-oven workers: 30 years of follow-up. *J. occup. Med.* (1995). (In press).

DOLL, R., Cadmium in the human environment: closing remarks. *In:* G.F. Nordberg, R.F.M. Herber and L. Alessio (eds.), *Cadmium in the human environment. Toxicity and carcinogenicity,* pp. 450–464, IARC, Lyon (1992).

ENTERLINE, P.E., HARTLEY, J. and HENDERSON, V., Asbestos and cancer: a cohort followed up to death. *Brit. J. ind. Med.*, **44,** 396–401 (1987).

FINN, B. and HALLENBECK, W.H., Detection of chrysotile asbestos in workers' urine. *Amer. ind. Hyg. Ass. J.,* **46,** 162–169 (1985).

HARD, G.C., RODGERS, I.S., BAETCKE, K.P., RICHARDS, W.L., MCGAUGHY, R.E. and VALCOVIC, L.R., Hazard evaluation of chemicals that cause accumulation of 2μ-globulin, hyaline droplet nephropathy and tubule neoplasia in the kidneys of male rats. *Environ. Health Perspect.,* **99,** 313–349 (1993).

HUANG, J., HISANGA, N., SAKAI, K., IWATA, M., ONO, Y., SHIBATA, E. and TAKEUCHI, Y., Asbestos fibers in human pulmonary and extrapulmonary tissues. *Amer. J. ind. Med.,* **14,** 331–339 (1988).

INTERNATIONAL LABOUR OFFICE, *International Standard Classification of Occupations,* ILO, Geneva (revised edition 1968, 1988).

KADAMANI, S., ASAL, N.R. and NELSON, R.Y., Occupational hydrocarbon exposure and risk of renal-cell carcinoma. *Amer. J. ind. Med.,* **15,** 131–141 (1981).

KANAZAWA, K., BIRBECK, M.S., CARTER, R.L. and ROE, F.J.C., Migration of asbestos fibers from subcutaneous injection sites in mice. *Brit. J. Cancer,* **24,** 96–106 (1970).

KOLONEL, L., Association of cadmium with renal cancer. *Cancer,* **37,** 1782–1787 (1976).

KREIGER, N., MARRETT, L.D., DODDS, L., HILDITCH, S. and DARLINGTON, G.A., Risk factors for renal-cell carcinoma: results of a population-based case-control study. *Cancer Causes Control,* **4,** 101–110 (1993).

LYNGE, E. and THYGESEN, L., Occupational cancer in Denmark: cancer incidence in the 1970 census population. *Scand. J. Work Environ. Health,* **16C** (Suppl 2), 6–35 (1990).

MACLURE, M., Asbestos and renal adenocarcinoma: a case-control study. *Environ. Res.,* **42,** 353–361 (1987).

MCFARLAND, H.N., ULRICH, C.E., HOLDSWORTH, C.E., KITCHEN, D.N., HALLIWELL, W.H. and BLUM, S.C., A chronic inhalation study with unleaded gasoline vapor. *J. Amer. Coll. Tox.,* **3,** 231–248 (1984).

MCLAUGHLIN, J.K., Renal-cell cancer and exposure to gasoline. *Environ. Health Perspect.,* **101** (Suppl. 6), 111–114 (1993).

MCLAUGHLIN, J.K., BLOT, W.S., MEHL, E.S., STEWART, P.A., VENABLE, F.S. and FRAUMENI, J.F., JR., Petroleum-related employment and renal-cell cancer. *J. occup. Med.,* **57,** 672–674 (1985).

MCLAUGHLIN, J.K., GAO, Y.T., GAO, R.N., ZHANG, W., JI, B.T. and BLOT, W.T., Risk factors for renal-cell cancer in Shanghai, China. *Int. J. Cancer,* **52,** 562–565 (1992).

MCLAUGHLIN, J.K., MALKER, H.S.R., STONE, B.J., WEINER, J.A., MALKER, B.K., ERICSSON, J.L.E., BLOT, W.J. and FRAUMENI, J.F., JR., Occupational risks for renal cancer in Sweden. *Brit. J. ind. Med.,* **44,** 119–123 (1987).

MCLAUGHLIN, J.K., MANDEL, J.S., BLOT, W.J., SCHUMAN, L.M., MEHL, E.S. and FRAUMENI, J.F. JR., A population-based case-control study of renal-cell carcinoma. *J. nat. Cancer Inst.,* **72,** 275–284 (1984).

MCLAUGHLIN, J.K., MELLEMGAARD, A., LINDBLAD, P., MCCREDIE, M., MANDEL, J.S., SCHLEHOFER, B. and POMMER, W., International renal-cell cancer study. I. Tobacco use. *Int. J. Cancer* **60,** 194–198 (1995).

PARTANEN, T., HEIKKILA, P., HERNBERG, S., KAUPPINEN, T., MONETA, G. and OJAJAWI, A., Renal-cell cancer and occupational exposure to chemical agents. *Scand. J. Work Environ. Health,* **17,** 231–239 (1991).

REDMOND, C.K., WIEAND, H.S., ROCHETTE, H.E., SASS, R. and WEINBERG, G., Long-term mortality experience of steelworkers. US-DHHS, PHS, CDC, NIOSH Publications 81-120, National Institute for Occupational Health and Safety, Cincinnati, Ohio (1981).

SELIKOFF, I.J., HAMMOND, E.C. and SEIDMAN, H., Mortality experience of insulation workers in the United States and Canada, 1943–1976. *Ann. N.Y. Acad. Sci.,* **330,** 91–116 (1979).

SHARPE, C.R., ROCHON, J.E., ADAM, J.M. and SUISSA, S., Case-control study of hydrocarbon exposures in patients with renal-cell carcinoma. *Canad. med. Ass. J.,* **140,** 1309–1318 (1989).

SIEMIATYCKI, J., DEWAR, R., NADON, L., GERIN, M., RICHARDSON, L. and WACHOLDER, S., Associations between several sites of cancer and twelve petroleum-derived liquids. *Scand. J. Work Environ. Health,* **13,** 493–504 (1987).

SMITH, A.H., SHEARN, V.I., WOOD, R., Asbestos and kidney cancer: the evidence supports a causal association. *Amer. J. ind. Med.,* **16,** 159–166 (1989).

SNOW, E.T., Metal carginogenesis, mechanistic implications. *Pharm. Ther.,* **53,** 31–65 (1992).

SPIRTAS, R., STEWART, P.A., LEE, J.S., MARANO, D.E., FORBES, C.D., GRAUMAN, D.J., PETTIGREW, H.M., BLAIR, A., HOOVER, R.N. and COHEN, J.L., Retrospective cohort mortality study of workers at an aircraft maintenance facility. I. Epidemiological results. *Brit. J. ind. Med.,* **48,** 515–530 (1991).

THUN, M.J., SCHNORR, T.M., SMITH, A.B., HALPERIN, W.E. and LEMEN, R.A., Mortality among a cohort of US cadmium-production workers—an update. *J. nat. Cancer Inst.,* **74,** 325–333 (1985).

UNITED NATIONS DEPARTMENT OF ECONOMIC AND SOCIAL AFFAIRS, UN STATISTICAL OFFICE, *International Standard Industrial Classification of All Economic Activities,* UN, New York (1968, 1971, 1990).

US DEPARTMENT OF COMMERCE, *Standard Occupational Classification Manual,* U.S. Government Printing Office, Superintendent of Documents, Washington, D.C. (1980).

US OFFICE OF MANAGEMENT AND BUDGET, *Standard Industrial Classification Manual,* Executive Office of the President, OMB, Washington, D.C. (1987).

YU, M.C., MACK, T.M., HANISCH, R., CICIONI, C. and HENDERSON, B.E., Cigarette smoking, obesity, diuretic use and coffee consumption as risk factors for renal-cell carcinoma. *J. nat. Cancer Inst.,* **77,** 351–356 (1986).