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Renal cell cancer and occupational exposure to chemical agents

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A case-referent study of occupational risk indicators of renal cell adenocarcinoma was conducted. Each incident case in Finland in 1977-1978 was matched with two population referents. Lifelong job histories were collected and translated into indicators of industry, occupation, and occupational exposures. The analyses of 338 sets of cases and referents revealed elevated risks for a history of employment in white-collar occupations; the printing industry; the chemical industry; the manufacturing of metal products; mail, telephone, and telegraph services; and iron and metalware work. A decreased risk was observed for male farmers. An elevated risk and an exposure-response relationship were found for gasoline exposure. The excess risk was highest at a latency period of approximately 30 years. The findings support the hypothesis that exposure to some constituent(s) of gasoline increases the incidence of renal adenocarcinoma in humans. Suggestions of elevated risks appeared for exposures to inorganic lead, cadmium, and nonchlorinated solvents.

Key terms: cadmium, case-referent study, gasoline, industries, lead, occupations, solvents.

Subjects and methods

The risk of contracting renal cell cancer was studied in relation to industrial categories, occupational titles, and occupational exposures in a case-referent study among Finnish residents over the age of 20 years at diagnosis. The objective of this study was to provide further insight into the occupational etiology of renal cell cancer.

The occupational determinants of renal cancer are poorly understood. Although several epidemiologic studies (1—23) have related specific industries and occupations with the risk of renal cell cancer, no consistent pattern emerges from these studies. Epidemiologic and experimental evidence has brought forth hypotheses on presumed work-related determinants of renal cell cancer. Those of primary concern are various hydrocarbon derivatives (24—26), petrochemicals and gasoline, jet fuel and other products of petroleum refining (16, 27—29); gasoline exhaust (18, 30); cadmium (31); inorganic lead compounds (10, 32); and asbestos (21, 22, 33).

The objective of this study was to provide further insight into the occupational etiology of renal cell cancer.

The mean age, at diagnosis, of the eligible cases and their referents was 63 (range 26—95) years. The women were older than the men by 2.4 years on the average.

The questionnaire requested information on the different jobs held, time periods of employment, and the identification of employers. This information enabled the reconstruction of the individual occupational histories on an annual basis. The histories were coded, year by year, into industries and occupational cate-

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Table 1. Distribution of the identified subjects, respondents, and those ever in worklife among the cases of primary renal cell carcinoma and their referents, by vital status.

| Vital status | Number of identified subjects | Respondents | Response rate (%) | Number ever in worklife |
|--------------|-------------------------------|-------------|------------------|------------------------|
| Alive        |                               |             |                  |                        |
| Cases        | 140                           | 99          | 7                | 106                    | 75.7                   | 98                      |
| Referents    | 280                           | 215         | 5                | 220                    | 78.6                   | 195                     |
| All          | 420                           | 314         | 12               | 326                    | 77.6                   | 293                     |
| Deceased     |                               |             |                  |                        |
| Cases        | 532                           | 330         | 25               | 355                    | 66.7                   | 310                     |
| Referents    | 1064                          | 655         | 40               | 695                    | 65.3                   | 624                     |
| All          | 1596                          | 985         | 65               | 1050                   | 65.8                   | 934                     |
| All          | 2016                          | 1299        | 77               | 1376                   | 68.3                   | 1227                    |

Table 2. Definitions of background, low, and high level of exposure for the different agents. [OEL = occupational exposure limit (36)]

| Agent                                    | Exposure level                     |
|------------------------------------------|------------------------------------|
| Asbestos (fibres/cm³)                    | Background: <0.1                   |
|                                          | Low: 0.1—1                         |
|                                          | High: >1                           |
| Animals                                  | Farmers with livestock              |
|                                          | Butchers, cattle tenders            |
| Cadmium and cadmium compounds (mg/m³)    | Background: <0.001                  |
|                                          | Low: 0.001—0.01                     |
|                                          | High: >0.01                         |
| Lead and inorganic lead compounds (mg/m³)| Background: <0.001                 |
|                                          | Low: 0.001—0.05                     |
|                                          | High: >0.05                         |
| Oil mist (mg/m³)                         | Background: <0.1                    |
|                                          | Low: 0.1—3                         |
|                                          | High: >3                            |
| Nonchlorinated solvents                  | Background: <0.02 × OEL             |
|                                          | Low: (0.02—1) × OEL                 |
|                                          | High: >OEL                          |
| Gasoline (ppm benzene)                   | Background: <0.1                   |
|                                          | Low: 0.1—1                         |
|                                          | High: >1                            |
| Diesel fuel and other distilled fuel oils| Operators of diesel-driven vehicles|
|                                          | Mechanics of diesel-driven vehicles,|
|                                          | etc                                 |
| Polycyclic aromatic hydrocarbons (µg/m³)| Background: <0.01                  |
|                                          | Low: 0.01—1                        |
|                                          | High: >1                           |

* The concentrations given are approximate guideposts rather than precise values.

The level of exposure was classified as low or high if the levels given in table 2 were considered to exist longer than 30% of the normal annual worktime. The concentrations defining the different levels of exposure formed approximate guideposts rather than precise figures.
In the gasoline vapor, calculated across all the years period 1920-1977), (ii) the total duration of exposure (in years) in the same period, (iii) the cumulative exposure (ppm-years = product of mean level and duration), and (iv) the latency period (1978 minus year of first recorded exposure).

### Results

#### Nonoccupational confounders

The odds ratio was 1.3 (95% CI 0.9—1.8) for smoking (ever), 1.2 (95% CI 0.9—1.7) for obesity (slightly overweight or obese), and 1.0 (95% CI 0.7—1.4) for coffee consumption (heavy). For women, the odds ratio for heavy coffee consumption was 1.4 (95% CI 0.7—2.8). While no statistically significantly elevated OR estimates were obtained, control for possible confounding due to these factors was considered prudent.

#### Industries and occupational categories

The odds ratios associated with employment or self-employment for at least five years in selected industries and occupations in the period 1920—1968 are summarized in tables 3 (men) and 4 (women). The selection of the industrial and occupational categories was done on the basis of a minimum of two cases in the industry or occupation. In addition, some industrial and occupational subcategories were not analyzed because we postulated that they did not involve any conceivable determinants of renal cell cancer.

Among industries, a statistically significantly depressed risk was observed for male farmers. Excess risks were observed for both the men and women employed in the printing and publishing industry, for the men employed in chemical and related industries, for the men employed in the manufacturing of metal products, machinery, and equipment, and for both the men and women in mail, telephone and telegraph services. For the mail, telephone and telegraph services, the OR pooled over the two genders was 4.9 (95% CI 1.3—18.4).

Among occupations, a significant excess risk was associated with the aggregate category of technical artistic, administrative, managerial and clerical occupations for the men but not for the women. A statistically significant deficit occurred for the men in agricultural occupations but not for the women. Elevated OR estimates were associated with men in iron and metalware occupations and with men in graphic work. The latter excess was concentrated in the small subgroup of printers (OR 6.0).

#### Occupational exposures

Table 5 shows the OR estimates for the different occupational exposures for the men and women combined, unadjusted for any confounders. Gasoline exposure was significantly associated with the risk of renal cell cancer. The OR estimates for cadmium, lead, and nonchlorinated solvents were elevated, but not statistically significantly so. In the subpopulation of blue-collar occupations (white-collar and farming occupations being excluded), the OR for lead and lead compounds was 5.2 (95% CI 0.5—6.5) as compared with 2.9 for the entire data, for nonchlorinated solvents it was 4.5 (95% CI 0.9—22.2) compared with

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2.9, for gasoline it was 3.6 (95% CI 1.4—9.2) compared with 1.7, and for PAH it was 4.4 (95% CI 0.4—43.1) compared with 1.1. The higher OR estimates for the blue-collar occupations indicate a negative confounding in the aggregate data due to social class and agricultural occupation or rural/urban gradient.

As the conditions of exposure might have been different for the men and women, the OR estimates for the different exposures were calculated separately for the two genders. For the men (table 6), the OR estimates adjusted for the nonoccupational confounders were similar to the unadjusted OR estimates for both genders combined (table 5). When the white-collar and farming occupations were excluded, the OR for asbestos was 1.6 (95% CI 0.4—6.0) compared with 0.9 for the entire data, for lead and lead compounds it was 5.6 (95% CI 0.6—54.8) compared with 2.8, for non-chlorinated solvents it was 4.8 (95% CI 1.0—23.8) compared with 3.5, for gasoline it was 3.9 (95% CI 1.4—10.6) compared with 1.6, and for PAH it was 5.5 (95% CI 0.5—58.9) compared with 1.2.

Among the women, the only exposure with a sufficient number of exposed subjects was the category of animal exposures. The OR, adjusted for confounding by smoking, coffee consumption, and obesity, was 1.3 (95% CI 0.8—2.2).

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### Table 3. Odds ratio (OR) estimates and their 95% confidence intervals (95% CI) for men in selected industries and occupations.

| Industry | Cases in the industry/occupation (N) | OR   | 95% CI   |
|----------|--------------------------------------|------|----------|
| Agriculture, hunting, forestry, fishing | 75 | 0.77 | 0.52—1.15 |
| Agriculture and hunting | 58 | 0.63 | 0.42—0.94 |
| Forestry and logging | 20 | 0.99 | 0.53—1.86 |
| Manufacturing | 56 | 1.34 | 0.84—2.13 |
| Food, beverages, tobacco | 5 | 1.05 | 0.33—3.31 |
| Textile, wearing apparel, leather | 2 | 0.88 | 0.12—6.46 |
| Wood (except furniture) | 10 | 0.96 | 0.42—2.20 |
| Paper and pulp; printing and publishing | 18 | 2.20 | 1.02—4.72 |
| Paper and paper products | 13 | 1.69 | 0.73—3.91 |
| Printing and publishing | 6 | 4.63 | 0.91—23.5 |
| Chemicals; chemical, petroleum, coal, rubber and plastic products | 8 | 4.19 | 1.09—16.1 |
| Nonmetallic mineral products (except petroleum and coal) | 2 | 0.51 | 0.09—2.75 |
| Metal products, machinery and equipment | 23 | 1.81 | 0.95—3.48 |
| Electricity, gas, water | 3 | 0.58 | 0.09—3.62 |
| Construction | 23 | 1.59 | 0.79—3.19 |
| Building | 16 | 1.25 | 0.57—2.70 |
| Earth improvement: excavating and foundation work; construction of highways, streets, airports, etc | 10 | 1.90 | 0.73—4.93 |
| Trade, restaurants, hotels | 25 | 1.44 | 0.78—2.67 |
| Transport, storage, communications | 26 | 1.24 | 0.70—2.18 |
| Transport and storage | 23 | 1.13 | 0.63—2.02 |
| Mail, telephone and telegraph services | 4 | 3.83 | 0.67—21.8 |
| Financing, real estate and business services | 6 | 2.58 | 0.83—10.5 |
| Community, social and personal services | 31 | 1.28 | 0.74—2.23 |
| Social, health care and related services | 5 | 0.51 | 0.18—1.45 |

### Table 4. Odds ratio (OR) estimates and their 95% confidence intervals (95% CI) for women in selected industries and occupations.

| Industry | Cases in the industry/occupation (N) | OR   | 95% CI   |
|----------|--------------------------------------|------|----------|
| Agriculture, hunting, forestry, fishing | 60 | 0.96 | 0.55—1.66 |
| Agriculture and hunting | 59 | 0.96 | 0.56—1.65 |
| Manufacturing | 19 | 1.08 | 0.54—2.15 |
| Textiles, leather | 10 | 1.68 | 0.66—4.31 |
| Paper and pulp; printing and publishing | 7 | 5.95 | 1.21—29.2 |
| Printing and publishing | 5 | 8.01 | 0.92—69.8 |
| Trade, restaurants, hotels | 19 | 1.29 | 0.63—2.66 |
| Transportation, storage, communications | 8 | 2.75 | 0.68—11.1 |
| Mail, telephone and telegraph services | 6 | 6.58 | 0.75—57.4 |
| Community, social and personal services | 18 | 0.83 | 0.43—1.64 |
| Social, health care and related services | 6 | 0.80 | 0.28—2.34 |

### Occupation

| Occupation | Cases in the industry/occupation (N) | OR   | 95% CI   |
|------------|--------------------------------------|------|----------|
| Technical, physical science, social science, humanistic, artistic work; administrative, managerial and clerical work | 42 | 1.97 | 1.19—3.26 |
| Sales work | 14 | 0.90 | 0.44—1.84 |
| Agriculture, forestry, fishing | 71 | 0.68 | 0.45—1.02 |
| Transportation | 21 | 1.09 | 0.59—2.00 |
| Manufacturing and related work | 78 | 1.33 | 0.87—2.04 |
| Iron and metalware work | 22 | 1.87 | 0.94—3.76 |
| Machinists; machine and engine repairmen | 10 | 2.33 | 0.83—6.51 |
| Woodwork | 15 | 0.79 | 0.40—1.56 |
| Graphic work | 6 | 4.89 | 0.97—24.7 |
| Printers | 4 | 5.96 | 0.85—54.5 |
| Chemical processing and related work | 5 | 1.43 | 0.41—5.03 |
| Stationary engine and motorpower work | 7 | 0.63 | 0.26—1.62 |

* Contrast: ≥5 years/no employment during 1920—1968, linear adjustment for obesity, smoking and coffee consumption, conditional logistic regression.
**Table 5. Odds ratio (OR) estimates and their 95% confidence intervals (95% CI) for various occupational exposures of the men and women combined.**

| Exposure                              | Exposed cases (N) | OR    | 95% CI       |
|---------------------------------------|-------------------|-------|--------------|
| Asbestos                              | 15                | 1.00  | 0.49—2.05   |
| Animals                               | 58                | 0.93  | 0.63—1.39   |
| Cadmium and cadmium compounds         | 3                 | 4.37  | 0.44—43.0   |
| Lead and inorganic lead compounds     | 4                 | 2.89  | 0.52—16.1   |
| Oil mist                              | 10                | 1.10  | 0.47—2.53   |
| Nonchlorinated solvents               | 9                 | 2.89  | 0.86—9.74   |
| Gasoline                              | 39                | 1.72  | 1.03—2.87   |
| Diesel fuel and other distilled fuel oils | 21               | 1.20  | 0.63—2.27   |
| Polycyclic aromatic hydrocarbons      | 7                 | 1.10  | 0.39—3.09   |

* Contrast: at least 5 years of a high or low level of exposure before 1968 or less than 5 years of exposure but at least 1 year of high level of exposure during 1920—1968 versus background exposure, conditional logistic regression.

**Gasoline exposure**

The level of gasoline exposure was classified as high (h) for 11 cases (28% of the 39 exposed cases) and two referents (6% of the 36 exposed referents) and as low (l) for the remaining exposed cases and referents. The persons exposed to gasoline had worked as vehicle mechanics (N_h=5), operators of a relief-printing press (N_h=3), a rotogravure pressman cleaning cylinders with gasoline (N_h=1), a weigher of containers and trucks in an oil refinery (N_h=1), a road tanker driver (N_h=1), a service station attendant (N_l=1), a firefighter (N_l=1), taxi drivers (N_l=4), operators of other gasoline-driven vehicles (N_l=22).

The exposed referents were vehicle mechanics (N_h=1 and N_l=2), a press operator and foreman in a relief-printing shop (N_h=1), lumberjacks (N_h=2), a service station attendant (N_l=1), taxi drivers (N_l=7), operators of other gasoline-driven vehicles (N_l=22).

Three occupational exposures were associated with gasoline exposure in the data and may therefore have confounded the gasoline-renal cancer association [ie, diesel and other distilled fuel oils (positive correlation with gasoline exposure), oil mist (positive correlation with gasoline), and animal exposure (negative correlation with gasoline)]. To control for concomitant exposure to diesel and other distilled fuel oils, we calculated the OR estimates for the persons with exposure to different combinations of gasoline, diesel, and other distilled fuel oils (table 7). Those exposed to gasoline in the absence of exposure to diesel and other distilled fuel oils exhibited the highest OR (2.1, 95% CI 1.1—4.0), while the OR for those with exposure to diesel and other distilled fuel oils only was 0.7.

**Table 6. Odds ratio (OR) estimates and their 95% confidence intervals (95% CI) for the occupational exposures of the men.**

| Exposure                              | Exposed cases (N) | OR    | 95% CI       |
|---------------------------------------|-------------------|-------|--------------|
| Asbestos                              | 14                | 0.94  | 0.45—1.97   |
| Animals                               | 16                | 0.67  | 0.35—1.31   |
| Cadmium and cadmium compounds         |                   |       |              |
| Lead and inorganic lead compounds     |                   |       |              |
| Oil mist                              |                   |       |              |
| Nonchlorinated solvents               |                   |       |              |
| Gasoline                              |                   |       |              |
| Diesel fuel and other distilled fuel oils |                |       |              |
| Polycyclic aromatic hydrocarbons      | 7                 | 1.21  | 0.43—3.45   |

* Contrast: at least 5 years of a high or low level of exposure before 1968 or less than 5 years of exposure but at least 1 year of high level of exposure during 1920—1968 versus background exposure, linear adjustment for obesity, smoking and coffee consumption, conditional logistic regression.

**Table 7. Odds ratio (OR) estimates and their 95% confidence intervals (95% CI) for combinations of the men’s exposures to gasoline and diesel and other distilled fuel oils.**

| Exposure combination                  | Exposed cases (N) | OR    | 95% CI       |
|---------------------------------------|-------------------|-------|--------------|
| No gasoline; no diesel or other       |                   |       |              |
| distilled fuel oil                    |                   |       |              |
| Gasoline only                         | 23                | 2.05  | 1.05—3.98   |
| Diesel or other distilled fuel only   | 6                 | 0.68  | 0.23—2.01   |
| Both                                  | 13                | 1.29  | 0.55—3.02   |

* Exposure = at least 5 years of a high or low level of exposure before 1968 or less than 5 years of exposure but at least 1 year of high level of exposure during 1920—1968.

**Next, the exposure-response gradients for gasoline exposure were scrutinized. The sparseness of the data did not allow for the simultaneous analysis of the mean level, duration, cumulated exposure, and latency period of gasoline exposure. We therefore performed four separate conditional logistic regressions entering one exposure dimension at a time. The distribution of the cases and referents along the four dimensions was unevenly spaced. To increase the stability of the esti-
Table 8. Fitted odds ratio (OR) estimates and their 95% confidence intervals (95% CI) for the level, duration, cumulative exposure, and latency period of gasoline exposure of the men. 

| Level (ppm equivalent of benzene) | Exposed cases (N) | OR    | 95% CI     |
|----------------------------------|-------------------|-------|------------|
| 0                               | 1                 |       |            |
| 0.1—0.19                        | 4                 | 0.63  | 0.19—2.12  |
| 0.2—0.9                         | 25                | 1.55  | 0.83—2.91  |
| 1.0—2.0                         | 10                | 7.39  | 1.58—34.6  |

| Duration (years) | Exposed cases (N) | OR    | 95% CI     |
|------------------|-------------------|-------|------------|
| 0                | 1                 |       |            |
| 5—11             | 13                | 1.39  | 0.61—3.13  |
| 12—20            | 13                | 2.02  | 0.83—4.90  |
| 21—51            | 13                | 1.58  | 0.69—3.63  |

| Cumulative exposure (ppm-years; benzene equivalent) | Exposed cases (N) | OR    | 95% CI     |
|---------------------------------------------------|-------------------|-------|------------|
| 0                                                 | 1                 |       |            |
| 0.5—1.9                                           | 7                 | 1.28  | 0.45—3.65  |
| 2.0—13                                            | 23                | 1.39  | 0.75—2.58  |
| 14—102                                            | 9                 | 4.34  | 1.15—16.4  |

| Latency (years) | Exposed cases (N) | OR    | 95% CI     |
|-----------------|-------------------|-------|------------|
| 0               | 1                 |       |            |
| 17—26           | 10                | 1.23  | 0.51—2.96  |
| 27—33           | 17                | 2.82  | 1.17—6.80  |
| 34—58           | 12                | 1.28  | 0.56—2.98  |

a Linear adjustment for obesity, smoking, and coffee consumption, conditional logistic regression.

Discussion

This report addresses the risk of renal cell cancer over industries, occupations, and occupational exposures. No strong ad hoc hypotheses of the chemical exposures as determinants of kidney cancer were set, with the possible exception of exposures to gasoline constituents and lead compounds.

The finding of an increased risk for men in the mixed category of different white-collar occupations is in agreement with results of a number of studies (1—4). The occupational exposures considered in this study were uncommon in the white-collar occupations. There was no clustering of cases into particular subcategories of industry or occupation among the men in white-collar occupations. Obesity, coffee consumption, or smoking did not explain the elevated risk.

In concordance with Danish (1) and Swedish (2) experience, a significant deficit in renal cancer risk was observed for male farmers.

The excess risk associated with employment in printing and publishing may be explained by gasoline exposure, which was fairly common in this industry, particularly among the men. In addition, exposure to lead and inorganic lead compounds was more frequent for the subjects in this industry than for the rest of the subjects. Both lead and, in particular, gasoline were associated with the risk of renal cell cancer, a finding in agreement with those of animal studies (27, 32). A related epidemiologic finding is that of Paganini-Hill et al (20), who reported a significantly increased mortality from kidney cancer among newspaper pressmen.

An increased risk was associated with the manufacturing of metal products, machinery, and equipment and iron and metalware work among the men. The exposures characterizing these jobs were cadmium, lead, oil mist, solvents, and PAH.

Men in the chemical, petroleum, coal, rubber, and plastics industries had an elevated risk but did not display anything unusual in the frequency of the exposures considered in this study. Closer scrutiny of this heterogeneous group revealed a cluster of three cases out of eight (but none among the referents) with a history of employment in the petroleum industry.

An excess risk was significantly associated with employment in mail, telephone, and telegraph services. No exposure under study was prominent in this industry. The represented occupations comprised postal van drivers, telephone and line installers, and various office jobs.

An elevated OR was observed for cadmium exposure among the men, but it was based on three cases only. The scanty prior evidence is restricted to a single epidemiologic study by Kolonel (31), who reported a significantly elevated OR for occupational exposure to cadmium in a case-referent study.

Lead acetate, lead subacetate, and lead phosphate have induced renal tumors in rats and mice by several routes of administration (32). Selavan and her collaborators (10) have reported elevated kidney cancer mortality for workers in a lead smelter. Two cases of renal cancer associated with heavy exposure to lead have also been reported (39, 40). Malcolm & Barnett
(41) observed an excess of deaths due to renal diseases among workers exposed to lead in factories producing lead acid batteries. Renal neoplasms were not mentioned by the authors. We found an elevated but statistically nonsignificant OR for exposure to lead and inorganic lead compounds. Of the high-risk industries and occupations, significantly elevated proportions of prior exposure to lead compounds was observed in printing and publishing and iron and metalware work. These findings are somewhat imprecise and do not therefore add much to the existing evidence for the hypothesis of an association between (inorganic) lead and renal cancer. The fact that the gasoline used in Finland, especially in the past, contains tetraethyl lead may be relevant in that gasoline exposure was associated with renal cancer risk. Tetraethyl lead is capable of dermal entrance to the organism, where a part of it is transformed into inorganic lead compounds (42). The amount of lead intake is probably low in the jobs with typical dermal exposure to gasoline, however.

Asbestos exposure has been related to an increased risk of kidney cancer in three epidemiologic studies (21, 22, 33). Asbestos fibers have been detected in the kidneys of exposed subjects (43, 44). Our results fail to substantiate these findings. The false negative rate of exposure assessment was probably highest for asbestos in our study. In addition, it is possible that the latency periods were insufficient, as the peak of asbestos use in Finland occurred around 1970. It would therefore seem that our OR estimate for asbestos was negatively biased. To the contrary, however, occupational titles with a high probability of asbestos exposure (dockyard workers, asbestos insulators, and workers in asbestos quarries, mills and asbestos product manufacturing facilities) were completely absent from our data. Our finding on asbestos is inconclusive.

We observed an elevated OR for nonchlorinated solvents for men. These solvents were constituents of paint and glue formulations (eg, toluene, xylenes, ketones, esters, alcohols, benzene, mineral spirit, and turpentine). The number of persons exposed to chlorinated solvents was too small for statistical analysis. It might be noted that Duh & Asal (12), Katz & Jowett (13), and Asal et al. (29), who found an elevated kidney cancer risk among laundry and dry-cleaning workers, did not discriminate between petroleum-based and chlorinated solvents as possible risk factors. There was only one case in our data with a history of dry-cleaning work (as an operator).

Gasoline exposure was consistently related to kidney cancer risk in our data. It persisted after control for obesity, smoking, coffee consumption, concomitant diesel fuel exposure, social status, and farming occupations. An exposure-response relation was observed for the level of exposure to gasoline, and a weaker such relation was seen for the cumulative exposure (product of mean level and duration). Duration of exposure alone was not linearly associated with the risk of renal cancer, a finding which might reflect the correlatedness between latency and duration, the latency peak appearing at the intermediate category of around 30 years. The composition of the imported gasoline used in Finland in the late 1940s and early 1950s is not well known. Tetraethyl lead was used as an anti-knock additive.

Regarding the assessment of some individual exposures to gasoline, the printing press operators (three cases and a referent) used gasoline as a cleaning agent in typographic printing shops. This use was confirmed by nurses and safety personnel of the printing shops concerned. The gasoline exposure (classified as low level) of a firefighter was based on the reporting of the case himself. The exposure of the operators of gasoline-driven vehicles, taxis included, was classified as low level, as their gasoline exposure was considered higher than in the population at large.

Our results suggest that some hydrocarbon constituent(s) or additive(s) of gasoline are conducive to renal cell cancer in humans. The level of exposure is probably important, and the postulated average latency period was about 30 years for the exposure conditions encountered in this study. Epidemiologic studies conducted elsewhere have, however, failed to produce convincing evidence of a relationship between gasoline exposure and renal cell cancer, with the possible exception of aviation gasoline reported by Siemiatycki and his co-workers (28). A suggestion of an exposure-response relationship between the duration of employment as a gasoline station attendant and the incidence of renal cell cancer has been reported by McLaughlin and his co-workers (23). The implicated dose-response relationship between unleaded gasoline and kidney cancer for the male rat (27) suggests some gasoline hydrocarbon(s) as responsible for the conjectured causal association. However, this finding may also be due to a male rat-specific protein (alpha-2-microglobulin) in the kidney, accumulated in the male rat as a result of exposure to a nephrotoxic hydrocarbon (2,2,4-trimethylpentane), a typical component of gasoline (45—47). The role of lead compounds cannot be ruled out when human exposure is under consideration.

Some remarks on the validity of the study are warranted. The misclassification rates of exposures were probably nondifferential between the cases and the referents because the coder was blinded to the case-referent status of the subjects. Since the subjects were matched for gender, age, and vital status, the probability of differential misclassification of exposures due to the matching factors (eg, old age) should be low. Every effort was undertaken to avoid, in the scoring of the exposures, false positive misclassifications of exposures, which would have been particularly prone to bias the OR estimates towards unity. High rates of false negative misclassification would however have the same effect, which may be reflected in our result for asbestos exposure. Some nondifferential misclassification may however have been possible by random
fluctuation when the number of exposed persons was small.

Nonresponse would bias the effect estimates if it were differentially correlated with industries, occupations, and exposures between the cases and referents. This possibility could not be directly checked. We cannot however envisage any reason why the referents exposed, for example, to gasoline would tend to refrain from replying, as compared with the cases. Insofar as nonresponse and the accuracy of work histories are dependent on age, gender, and the data source (self or next-of-kin), the matching that was performed should preclude information bias from these sources. The exclusions of subjects due to incomplete case-referent sets in the conditional analyses were in all likelihood randomly distributed between the cases and referents in occupational categories and exposures. We therefore believe there was no serious bias introduced by these exclusions. The exclusion of all subjects with no reported occupational history was a deliberate restriction of the source population, as those without such a history were noninformative in the study base, which was designed to address occupational exposures.

In conclusion, the most important finding of this study is the qualitative and quantitative evidence contributing credence to the hypothesis that exposure to some constituent(s), hydrocarbons, or additives of gasoline increases the risk of renal adenocarcinoma in humans. Our data do not allow for further chemical specification of this hypothesis.

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