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# Kidney Cancer and Hydrocarbon Exposures among Petroleum Refinery Workers

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**To evaluate the hypothesis of increased kidney cancer risk after exposure to hydrocarbons, especially those present in gasoline, we conducted a case–control study in a cohort of approximately 100,000 male refinery workers from five petroleum companies. A review of 18,323 death certificates identified 102 kidney cancer cases, to each of whom four controls were matched by refinery location and decade of birth. Work histories, containing an average of 15.7 job assignments per subject, were found for 98% of the cases and 94% of the controls. To each job, industrial hygienists assigned semiquantitative ratings for the intensity and frequency of exposures to three hydrocarbon categories: nonaromatic liquid gasoline distillates, aromatic hydrocarbons, and the more volatile hydrocarbons. Ratings of "present" or "absent" were assigned for seven additional exposures: higher boiling hydrocarbons, polynuclear aromatic hydrocarbons, asbestos, chlorinated solvents, ionizing radiation, and lead. Each exposure had either no association or a weak association with kidney cancer. For the hydrocarbon category of principal *a priori* interest, the nonaromatic liquid gasoline distillates, the estimated relative risk (RR) for any exposure above refinery background was 1.0 (95% confidence interval [CI] 0.5–1.9). Analyses of cumulative exposures and of exposures in varying time periods before kidney cancer occurrence also produced null or near-null results. In an analysis of the longest job held by each subject (average duration 9.2 years or 40% of the refinery work history), three groups appeared to be at increased risk: laborers (RR = 1.9, 95% CI 1.0–3.9); workers in receipt, storage, and movements (RR = 2.5, 95% CI 0.9–6.6); and unit cleaners (RR = 2.3, 95% CI 0.5–9.9).**

## Introduction

Male rats exposed by inhalation to wholly vaporized, unleaded gasoline experienced a dose-related increase in kidney cancer incidence, which was not observed among female rats or mice of either gender (*1–3*). A reversible, nongenotoxic nephropathy produced by exposure to certain hydrocarbons, especially branched alkanes with six or more carbon atoms ($C_6+$ isoalkanes), appears to be responsible for this effect (*4–6*).

As summarized in several comprehensive reviews (*7–12*), more than 20 epidemiologic studies have compared death rates from kidney cancer (including cancers of the renal pelvis and ureter as well as renal cell cancer) among petroleum industry employees with national or regional rates. Wong and Raabe (*12*) computed a summary standardized mortality ratio of 1.0 (95% confidence interval [CI] 0.8–1.2). In general, these studies are limited by a lack of exposure information, with index or exposed groups defined no more specifically than as petroleum industry employees.

A smaller number of kidney cancer case–control studies in general populations have examined employment in occupations involving exposures to petroleum hydrocarbons (*13–19*). These studies are limited by the low prevalence of occupational hydrocarbon exposure in the general population and by the need to rely on interviews or questionnaires for exposure information. One large study, with 313 male cases, reported a relative risk (RR) of 1.7 (CI 1.0–2.9) for self-reported exposures to petroleum, tar, and pitch products (*13*). A more detailed analysis of occupational histories in the same study produced an estimated RR of 1.0 (CI 0.7–1.4) for ever having worked in petroleum-related occupations (*14*). For employment as a gasoline station attendant, the estimated RR was 1.2 (CI 0.6–2.3), with an unstable trend toward higher RRs with longer employment. Another sizable study, with 142 male cases, reported an RR of 1.6 for any occupational hydrocarbon exposure (CI 0.8–3.2), with higher RRs among men exposed for more than 15 years (*18*). A more recent study, with 408 male and female cases, reported an RR of 1.7 (CI 1.0–2.9) for at least 5 years of high- or low-level gasoline exposure or at least 1 year of high-level gasoline exposure

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occurring more than 10 years before diagnosis (*19*). Among men, the estimated RRs rose with a measure of cumulative exposure and were greatest for exposures in the period 27–33 years before diagnosis; comparable analyses were not presented for women. Results for hydrocarbon exposures were not published from a study with 473 male kidney cancer cases (*20*) because preliminary analyses revealed little or no association (M. Maclure, personal communication).

The present study was designed to extract more information from cohorts of petroleum industry employees than can be obtained from any single cohort or from meta-analyses of published results. The design is a case–control study in an aggregated cohort from several petroleum companies. The consolidation of cohorts enhances statistical precision and enables the consistent application of a single method of exposure assessment. The case–control design permits an examination of individual work histories at a level of detail that would not be feasible for the tens of thousands of members of the consolidated cohort.

# Subjects and Methods

## Assembly of Cohort

Cohorts of petroleum industry employees from 36 refinery locations (*21–27*) were consolidated into a combined cohort. In two of these cohorts (*21,26*), kidney cancer case–control studies had been conducted previously (*21,27*). The small numbers of women and petrochemical workers present in some of the original cohorts were excluded from the present study. The minimum employment duration criteria for cohort membership ranged from 6 months (*25*) to 5 years (*21*). Follow-up periods ranged from eight years (*23*) to 30 years (*21,23–27*) in length, with closing dates in the late 1970s or early 1980s for all studies. In the aggregate, the consolidated cohorts contributed 65% of the 147 kidney cancer deaths among petroleum industry employees identified in Wong and Raabe's literature survey (*12*).

## Case Ascertainment

The term "kidney cancer" in this report refers specifically to primary renal cell carcinoma, also known as adenocarcinoma of the kidney or hypernephroma. Malignant neoplasms stated on death certificates to have occurred in the renal pelvis, ureter, urethra, and paraurethral glands were excluded because most of the malignant tumors observed among the male rats experimentally exposed to gasoline were carcinomas of the renal parenchyma (*1–3*). Furthermore, in their histologic appearance and epidemiologic features, the excluded tumors resemble cancers of the urinary bladder much more closely than they resemble adenocarcinoma of the kidney (*29*).

To maximize and standardize case-finding, one of us (M.S.) read all 18,323 death certificates that had been collected through the most recent date of follow-up in each study. The search was for any mention of kidney cancer, as defined above, as opposed to only those deaths for which kidney cancer would be classified as the underlying cause. Every death certificate that appeared to identify a case, every certificate for which there was any question, and every 50th certificate were photocopied. The copies were reviewed and coded by an experienced nosologist. Only the cases confirmed by the nosologist were included in the study.

## Control Selection and Work History Retrival

The participating companies provided computer files of cohort rosters containing race, vital status at the close of follow-up, and dates of birth, hire, and termination of employment. A random sample of four controls was selected for each case within categories of the matching factors: employer and refinery location, decade of birth, and at-risk status. Matching by at-risk status simply means that each control was alive and free of a known diagnosis of kidney cancer at the estimated date of the case's diagnosis. The dates of diagnosis were estimated using age-specific kidney cancer survival data from the Third National Cancer Survey (*30*). Matching jointly by decade of birth and at-risk status is tantamount to matching by decade of age at the estimated date of diagnosis.

Copies of original work history records for all cases and controls were requested from the companies. If a control's work history could not be located, a supplemental control was selected from the remaining cohort members who met the same matching criteria. No additional controls were selected if a supplemental control's work history could not be found. The inclusion or exclusion of the supplemental controls had no discernible affect on the results of the analyses.

All entries on the work histories were transcribed verbatim onto a computer file. Each indication of a change of employment status, job title, department, or work location was considered a "job," as was each gap in the chronology.

## Exposure Assessment

Refinery exposures were considered in two categories. The primary exposures were defined as major categories of hydrocarbons, with an emphasis on creating a category that would classify subjects with respect to exposure to the hydrocarbons present in gasoline. The secondary exposures were defined as other chemical and physical agents that might be encountered in refinery work and that have been reported or hypothesized to be related to cancer in general or kidney cancer in particular.

Because gasoline is a complex mixture of several hundred hydrocarbons, it was feasible only to group exposures into broad categories. The principal purpose of the categorization was to enable work history information to be linked to specific refinery processes that could lead to exposures to qualitatively different types of hydrocarbons. The distillation temperature at atmospheric pressure proved to be a convenient property for this purpose because of its relation to hydrocarbon volatility and, therefore, to the potential for exposure by inhalation. A second property considered was chemical structure.

The result was a set of three primary hydrocarbon categories. The nonaromatic liquid gasoline distillates (NALGD), with an approximate distillation range of +40 to +200°C, was the category of principal interest because it contains the highly branched $C_6+$ isoalkanes, such as iso-octane. The lowest-boiling aromatic compounds (benzene, toluene and xylene) have a distillation range of approximately +80–+142°C, which falls within the NALGD range. These compounds were given separate consideration because of the well-known relation between benzene and leukemia. The third primary hydrocarbon category consisted of the more volatile hydrocarbons, with an approximate distillation range of −42–+40°C. These compounds, which include *n*-butane and iso-pentane, present the greatest potential for inhalation exposure because of their high vapor pressure under ordinary atmospheric conditions.

Seven secondary exposures were identified: higher-boiling hydrocarbons, polynuclear aromatic hydrocarbons (PAH), asbestos, chlorinated solvents, ionizing radiation, and lead. The mounting evidence on occupational asbestos exposure and kidney cancer has recently been reviewed (*31*). Three studies (*32–34*) have reported elevated kidney cancer mortality among laundry and dry-cleaning workers, who are exposed to a variety of chlorinated solvents, although a more recent study with improved methodology did not obtain a similar result (*35*). There also have been isolated reports of kidney cancer excesses in relation to the polynuclear aromatic hydrocarbons (PAH) present in coke oven emissions (*36*). Some nitrosamines are potent carcinogens in rodents (*37*). Ionizing radiation, of course, is associated with a wide variety of cancers (*38*). For completeness, lead and the hydrocarbons in the atmospheric distillation range above that of the NALGD category, approximately +200–+400°C, were added to the list; these higher-boiling hydrocarbons or "middle distillates" include heavy naphtha, kerosene, and light gas oil. For these exposures, each job was simply assigned a dichotomous rating denoting the agent's presence or absence.

For the primary hydrocarbon categories, each job was assigned two semiquantitative ratings: one for the intensity of exposure and another for exposure frequency. Each rating was on a three-point scale. The intensity rating was assigned first and was intended to represent the highest exposure level that would be encountered at least once a month in the given job. The rating procedure explicitly assumed that all remaining time on that job was spent at the next-lower intensity level.

The lowest intensity rating identified exposures judged to be at "refinery background." Refinery background exposures would be experienced by service or support personnel not directly involved in refinery operations, such as security guards and office workers. The highest rating was intended to capture exposures that, in the judgment of the participating industrial hygienists, fell into the upper one-fourth of all historical exposures at the refinery. The frequency ratings corresponded to daily, weekly, and monthly exposures at the assigned intensity level. In practice, the lowest frequency rating (monthly) was assigned to fewer than 0.1% of all jobs. These jobs were grouped for analysis along with the jobs that were assigned the same intensity rating and the intermediate (weekly) frequency rating.

Subjective confidence scores were assigned to all primary and secondary exposure ratings to indicate the degree of certainty the industrial hygienists were willing to place in their collective judgments. The three-category scoring scheme ranged, in colloquial terms, from speculative or "pure guesswork" to "educated guess" to "reasonably sure." Each job was also assigned codes to indicate the job title and refinery unit. These codes were based on a modification of a six-digit American Petroleum Institute coding system for refinery tasks and processes (available upon request, American Petroleum Institute, Washington, DC).

The exposure ratings were assigned during site visits to the refineries or company headquarters using a previously developed exposure assessment plan. The work history entries for all cases and controls from each refinery were arranged on the rating sheets chronologically within general job categories (e.g., all pipefitting jobs were grouped together). This arrangement achieved a masking of the case or control status of each job and made it easy for changes in processes or materials at specific points in the refinery's history to be reflected in the exposure ratings. The ratings were assigned by a team consisting of one of us (L.L.) and one or more experienced industrial hygienists from the company that owned the refinery. Current and former employees with intimate knowledge and long experience at the refinery location frequently provided key information, especially with respect to occasionally cryptic work history annotations and materials and processes that were no longer in use, but these persons did not participate in rating decisions.

## Data Reduction and Analysis

Scores were assigned to the exposure ratings for each job so that measures of cumulative exposure could be computed. For the secondary exposures, the scores were simply 1 for present and 0 for absent. Two secondary exposures were infrequently rated as present. Nitrosamines were judged to have been present in only one job, which was held by a control. Ionizing radiation was identified as present in 24 jobs for five subjects, all of whom were controls. Because of their low frequency, these two exposures were not considered in the data analysis.

For the primary hydrocarbon categories, three sets of scores were used (Table 1). Set 1, which was used in the main analyses, implied an equal difference in exposure from each intensity–frequency combination to the next in the rank ordering. Score sets 2 and 3 were used in ancillary analyses to test the sensitivity of the results to the assumption of linearity in set 1. In set 2, the incremental differences in actual exposure were assumed to be greater at the high end of the scale than at the low end. In score set 3, the differences were assumed to be greater at the low end of the scale than at the high end. For the NALGD hydrocarbon category, Table 1 shows the number of jobs to

**Table 1. Number of jobs, mean confidence score, and three sets of exposure scores for nonaromatic, liquid gasoline hydrocarbon category by combined ratings for exposure intensity and frequency.**

| Ratings for exposure intensity and frequency | No. of jobs | Mean confidence score[a] | Exposure score Set 1 | Exposure score Set 2 | Exposure score Set 3 |
|---|---|---|---|---|---|
| Never above refinery background | 3362 | 5.9 | 0.00 | 0.00 | 0.00 |
| Intermediate intensity, less often than daily | 1936 | 5.5 | 0.25 | 0.10 | 0.40 |
| Intermediate intensity, daily | 1990 | 5.8 | 0.50 | 0.30 | 0.70 |
| Relatively high intensity, less often than daily | 219 | 5.0 | 0.75 | 0.60 | 0.90 |
| Relatively high intensity, daily | 436 | 5.8 | 1.00 | 1.00 | 1.00 |
| Unknown[b] | 710 | NA | 0.00 | 0.00 | 0.00 |

NA, not applicable.

[a] The minimum combined confidence score is 2.0 ("pure guesswork" for both intensity and frequency of exposure). The maximum is 6.0 ("reasonably sure" about both intensity and frequency).

[b] Most "unknown" exposure assignments were gaps in work history chronologies (see text).

which each intensity–frequency combination was assigned, the mean confidence score, and the value of the exposure score from each of the three exposure-score sets.

For each exposure, the score assigned to a given job was multiplied by the length of time the job was held to create estimates of cumulative exposure in units of score-years. (Because the only possible job-specific ratings for the secondary exposures were 1 and 0, there was no difference between cumulative exposure and duration of exposure to these agents.) The score-years were then summed over all or a portion of the jobs in each person's work history. Summation over the whole work history produced a measure of cumulative exposure for the person's entire tenure of employment at the refinery. Because the highest exposure score in each set was 1.00, each person's highest possible number of score-years was equal to his duration of employment.

The score-years were also summed for each person within intervals of hypothetical kidney cancer induction time. These summations were computed by considering only the jobs that each case and his matched controls held within specific periods of time prior to the estimated date of the case's diagnosis. The highest possible number of score-years an individual could accumulate within an exposure interval was equal to the duration of that interval.

After the exposure rating system was developed and implemented, information became available to indicate an inverse association between the concentration of isoalkanes and the concentration of aromatic compounds in certain gasoline blend streams. Light straight-run naphtha is low in aromatics and alkylate naphtha is composed entirely of isoalkanes. Other gasoline blend streams are relatively high in aromatics, with moderate to equivalent levels of isoalkanes (R.C. Russell, Exxon Company USA, unpublished data). Commercial unleaded gasoline also appears to exhibit an inverse association between its aromatic content and its $C_6+$ isoalkane content (*39*). It is therefore possible that in some cases when the industrial hygienists assigned a lower rating for aromatics than for NALGD to a particular job, this combination of ratings might have reflected an NALGD exposure (e.g., for alkylate naphtha) that was relatively rich in $C_6+$ isoalkanes.

To explore this possibility, we devised a scheme to weight each NALGD exposure score in a manner that depended on the rating for aromatics that had been assigned to the same job. If exposure to aromatics was rated lower than NALGD exposure, according to the rank-ordering in Table 1, we multiplied the NALGD exposure score by four-thirds (1.33); if the aromatics rating was equal to or greater than the NALGD rating, we multiplied the NALGD exposure score by two-thirds (0.67). This weighting procedure had the effect of doubling the NALGD score for the jobs in which exposure to aromatics was rated as lower than NALGD exposure (with each exposure assessed on its own relative, historical scale). For instance, with the unweighted scores in score set 1 as the base (Table 1), the weighted scores for NALGD were 0.00, 0.33, 0.67, 1.00, and 1.33 when aromatics were rated lower than NALGD. When aromatics were rated equal to or higher than NALGD, the weighted NALGD scores in set 1 were 0.00, 0.17, 0.33, 0.50, and 0.67. By increasing the NALGD scores for some jobs and decreasing the scores for the others, this weighting system produced distributions of weighted NALGD score-years that were similar to the unweighted distributions.

An analysis of job titles and refinery units focused on the longest job assignment held by each case and control. These jobs were held for a mean of 9.2 years, or 40% of each subject's total duration of employment. On average, the longest job was the 12th job assignment on the work history. This job began an average of 11 years after the date of hire and ended an average of 13 years before termination of employment (or the estimated date of the matched case's diagnosis, whichever came first).

We grouped the job title and unit codes into eight general categories for the analysis of longest-held job. For the reference category, we compiled all the jobs of office workers and professional and technical staff into an administration and services category. Next, we created a category composed of workers in receipt, storage, and movements (excluding those who had already been identified as belonging in the administrative and services category). Monitoring data indicated that some jobs in these units, such as jobs in the transport and distribution of finished petroleum products, tend to entail higher hydrocarbon exposures than jobs in refining processes (*11,39,40*). The remaining categories were constructed by selecting common job titles with unit codes other than those that made up the previously defined categories. The most general categories were laborers and operators. The diverse maintenance and maintenance crafts category included sandblasters, carpenters, masons, painters, insulators, electricians and instrument men, boilermakers, welders, mobile equipment operators, and lead burners. Two job title codes from the maintenance crafts category were numerous enough for separate analysis: pipefitters and machinists (the latter category including blacksmiths). Finally, we created a category for the relatively small number of subjects whose longest jobs were as unit cleaners. In the exposure rating sessions, the industrial hygienists repeatedly singled out unit cleaners for their particularly high and nonspecific hydrocarbon exposures.

Conditional logistic regression analysis was used to control matched and unmatched covariates in producing estimates of RR. The only unmatched covariates available for analyses were race (white, nonwhite) and Spanish surname, as a marker of Hispanic ethnicity. Because control for these two variables never produced an appreciable change in the estimated RRs, the reported results were computed controlling only the matching factors. As can be seen by computing crude (i.e., unconditional) RR estimates from the case and control counts reported in the tables, control of the matching factors also had a negligible influence on the results.

Relative risks were estimated for any exposure above refinery background levels throughout each employee's entire work history and within the specified periods of hypothetical cancer induction time. Relative risks were also estimated for cumulative exposure to each of the primary and secondary exposures. In addition, RRs were computed for the longest jobs held by the cases and controls, within the previously described categories based on the assigned job title and unit codes. The precision of the RR estimates was assessed by means of 95% CIs.

## Results

The death certificate review produced 104 tentatively identified kidney cancer cases. The nosologist confirmed 102 (98%) as cases according to the definition established for the study. None of the questionable or systematically sampled death certificates was classified as a case.

Work histories could not be found for two (2%) of the 102 cases and 21 (5%) of the 408 original controls. Supplemental controls were selected for these 21 controls and for two controls whose work histories were truncated. The study thus contained a total of 23 supplemental controls, 19 of whose work histories were found.

Within the total of 506 work histories (100 cases and 406 controls), we found a total of 683 chronologic gaps. Nearly all were time periods during which the employee was known not to have been actively employed (e.g., he was laid off or on military or sick leave). At least one such gap was present in the work histories of 54% of the cases and 48% of the controls. The work histories of 10% of the cases and 10% of the controls had more than three gaps. The gaps ranged in length from 1 day to 23.1 years, with a mean of 1.1 years. Fifty-three percent of the gaps were for periods of 3 months or less, and 24% were for periods longer than 1 year.

Table 2 shows distributions of the subjects by variables other than refinery exposures. The cases and controls had very similar distributions of employment duration, age at termination of employment, year of termination, and age at the time of the case's diagnosis. These similarities are attributable to the matching of the cases and controls by decade of birth and "at-risk status" at the estimated date of diagnosis, which is tantamount to matching by decade of age. The distributions of year of hire were also nearly

**Table 2. Distributions of cases and controls by variables other than refinery exposures.**

| Variable | Cases | Controls | Variable | Cases | Controls |
|---|---|---|---|---|---|
| Age at hire, years | | | Age at termination, years | | |
| <20 | 10 | 58 | <40 | 11 | 45 |
| 20–24 | 31 | 113 | 40–44 | 3 | 27 |
| 25–29 | 23 | 102 | 45–49 | 8 | 37 |
| 30–34 | 19 | 64 | 50–54 | 11 | 44 |
| 35–39 | 6 | 48 | 55–59 | 25 | 110 |
| 40–44 | 6 | 24 | 60–64 | 29 | 114 |
| ≥45 | 7 | 22 | ≥65 | 15 | 54 |
| Year of hire | | | Age at case's diagnosis, years | | |
| <1920 | 15 | 59 | <50 | 17 | 74 |
| 1920–24 | 13 | 61 | 50–54 | 10 | 44 |
| 1925–29 | 20 | 68 | 55–59 | 14 | 81 |
| 1930–34 | 4 | 26 | 60–64 | 20 | 51 |
| 1935–39 | 10 | 43 | 65–69 | 10 | 70 |
| 1940–44 | 23 | 89 | 70–74 | 14 | 47 |
| ≥1945 | 17 | 85 | ≥75 | 17 | 64 |
| Employment duration, years | | | Year of termination | | |
| <10 | 14 | 65 | <1950 | 13 | 51 |
| 10–19 | 13 | 41 | 1950–54 | 11 | 43 |
| 20–29 | 23 | 122 | 1955–59 | 24 | 71 |
| 30–39 | 43 | 158 | 1960–64 | 17 | 72 |
| ≥40 | 9 | 45 | 1965–69 | 8 | 46 |
| | | | 1970–74 | 18 | 64 |
| | | | ≥1975 | 11 | 84 |

identical. The cases tended to have been hired at older ages than the controls, however. The RR associated with being hired at age 20 or older was 1.48 (CI 0.71–3.09). In comparison with being hired at younger than 20, the RR for beginning employment at age 45 or older was 1.92 (CI 0.58–6.37).

With respect to ever having held a job with an exposure rating above refinery background, the relative risks for all primary and secondary exposures were at or close to the null value (Table 3). Examination of cumulative exposure categories also produced near-null RRs, with no indication of regularity in exposure–response trends (Table 4). Analyses restricted to specified time periods prior to diagnosis produced no strong associations between kidney cancer and any of the primary hydrocarbon categories (Table 5).

We computed associations between kidney cancer and exposure to the NALGD category of hydrocarbons within categories of age at diagnosis, age at hire, and year of hire (Table 6). Because the numbers of cases and controls who had never had jobs rated at above refinery-background exposure levels were too small to support a meaningful analysis within categories of these variables, we divided

**Table 3. Relative risk for any above-background exposure to the primary and secondary exposures.**

| | Never exposed | | Ever exposed | | | |
|---|---|---|---|---|---|---|
| Exposure | Cases | Controls | Cases | Controls | Relative risk | 95% CI |
| Nonaromatic, liquid gasoline distillates | 13 | 53 | 87 | 353 | 1.00 | 0.51–1.94 |
| Aromatic hydrocarbons | 20 | 96 | 80 | 310 | 0.95 | 0.50–1.80 |
| Volatile hydrocarbons | 15 | 59 | 85 | 347 | 1.31 | 0.72–2.39 |
| Higher boiling hydrocarbons | 14 | 55 | 86 | 351 | 0.95 | 0.49–1.84 |
| Polynuclear aromatic hydrocarbons | 24 | 76 | 76 | 330 | 0.69 | 0.40–1.21 |
| Asbestos | 15 | 49 | 85 | 357 | 0.76 | 0.40–1.44 |
| Chlorinated solvents | 88 | 344 | 12 | 62 | 0.69 | 0.32–1.50 |
| Lead | 28 | 109 | 72 | 297 | 0.93 | 0.57–1.54 |

**Table 4. Relative risks within categories of cumulative exposure to the primary exposures.**

| | | | Score-years (score set 1) | | |
|---|---|---|---|---|---|
| Exposure | Group of measure | Never exposed | < 5 | 5–9 | ≥10 |
| Nonaromatic, liquid gasoline distillates (unweighted scores) | Cases | 13 | 41 | 22 | 24 |
| | Controls | 53 | 159 | 107 | 87 |
| | RR | 1.00 | 1.03 | 0.83 | 1.08 |
| | 95% CI | | 0.51–2.08 | 0.38–1.83 | 0.50–2.33 |
| Nonaromatic, liquid gasoline distillates (weighted scores) | Cases | 13 | 48 | 25 | 14 |
| | Controls | 53 | 204 | 87 | 62 |
| | RR | 1.00 | 0.96 | 1.20 | 0.89 |
| | 95% CI | | 0.48–1.92 | 0.55–2.61 | 0.38–2.09 |
| Aromatic hydrocarbons | Cases | 20 | 43 | 17 | 20 |
| | Controls | 95 | 145 | 93 | 73 |
| | RR | 1.00 | 1.45 | 0.91 | 1.30 |
| | 95% CI | | 0.76–2.77 | 0.42–1.99 | 0.62–2.73 |
| Volatile hydrocarbons | Cases | 15 | 46 | 23 | 16 |
| | Controls | 59 | 185 | 95 | 67 |
| | RR | 1.00 | 0.96 | 0.96 | 0.92 |
| | 95% CI | | 0.49–1.88 | 0.45–2.04 | 0.40–2.09 |

**Table 5. Relative risks for any above-background exposure to the primary exposures within time periods prior to diagnosis.**

| | | Never exposed | | Ever exposed | | | |
|---|---|---|---|---|---|---|---|
| Exposure | Years prior to diagnosis | Cases | Controls | Cases | Controls | Relative risk | 95% CI |
| Nonaromatic, liquid gasoline distillates | <10 | 51 | 220 | 49 | 186 | 1.25 | 0.74–2.11 |
| | 10–19 | 39 | 174 | 61 | 232 | 1.22 | 0.75–1.97 |
| | ≥20 | 33 | 107 | 67 | 299 | 0.64 | 0.36–1.11 |
| Aromatic hydrocarbons | <10 | 61 | 235 | 39 | 171 | 0.89 | 0.53–1.49 |
| | 10–19 | 47 | 191 | 53 | 215 | 1.03 | 0.64–1.65 |
| | ≥20 | 38 | 142 | 62 | 264 | 0.82 | 0.48–1.42 |
| Volatile hydrocarbons | <10 | 55 | 233 | 45 | 173 | 1.20 | 0.72–2.00 |
| | 10–19 | 45 | 190 | 55 | 216 | 1.06 | 0.69–1.79 |
| | ≥20 | 35 | 112 | 65 | 294 | 0.63 | 0.37–1.07 |

**Table 6. Relative risks for cumulative exposures to nonaromatic, liquid gasoline distillates within categories of age at diagnosis, age at hire and year of hire.**

| | < 5 score-years | | ≥5 score-years | | | |
|---|---|---|---|---|---|---|
| Variable | Cases | Controls | Cases | Controls | Relative risk | 95% CI |
| Age at diagnosis | | | | | | |
| <55 | 22 | 75 | 5 | 41 | 0.46 | 0.16–1.37 |
| 55–64 | 11 | 61 | 22 | 69 | 2.04 | 0.82–5.07 |
| 65–74 | 13 | 49 | 10 | 57 | 0.72 | 0.27–1.94 |
| ≥75 | 8 | 27 | 9 | 27 | 1.04 | 0.34–3.24 |
| Age at hire | | | | | | |
| <25 | 23 | 85 | 16 | 78 | 0.75 | 0.33–1.70 |
| 25–29 | 11 | 46 | 12 | 55 | 1.14 | 0.33–3.89 |
| 30–34 | 10 | 23 | 9 | 34 | 1.00 | 0.06–15.99 |
| ≥35 | 10 | 58 | 9 | 27 | 2.50 | 0.72–8.72 |
| Year of hire | | | | | | |
| <1925 | 13 | 44 | 14 | 64 | 1.04 | 0.38–2.84 |
| 1925–34 | 12 | 35 | 11 | 52 | 1.43 | 0.44–4.65 |
| 1935–44 | 18 | 79 | 15 | 48 | 1.29 | 0.51–3.29 |
| ≥1945 | 11 | 54 | 6 | 30 | 0.61 | 0.14–2.58 |

cumulative NALGD exposures at 5 score-years. An inverse association between exposure and disease among the youngest cases at diagnosis (<55 years) was balanced by a direct association in the next-older age group (55–64 years). A direct association was evident among cohort members who were relatively old at the time of hire (≥ 35 years). No strong associations were apparent within categories of year of hire.

In other analyses, we examined associations between kidney cancer and all three primary hydrocarbon categories, stratifying simultaneously by cumulative exposure and time prior to diagnosis. We also repeated the NALGD analyses using exposure score sets 2 and 3 and analyzed the secondary exposures within categories of exposure duration and time before diagnosis. No appreciably elevated relative risks were produced by any of these analyses.

Compared with employees whose longest jobs were in administration and services, operators and maintenance workers did not seem to differ in kidney cancer risk (Table 7). Machinists and pipefitters appeared to be at relatively low risk. Receipt, storage, and movements workers, laborers, and unit cleaners appeared to be at increased risk. Because of the small numbers of unit cleaners, the estimated RR of 2.3 for this job category was much less statistically stable than the others. Because most of the laborers (RR = 1.9) were assigned the most general unit codes, a more detailed analysis of this job category was impossible. The jobs in the receipt, storage, and movements category (RR = 2.5) were in the following units: pump (two cases and three controls); tank farms (one case and one control); water transport, wharf (two cases and one control); truck and rail transport (two cases and three controls); pipeline transport (no cases and two controls); and unspecified (two cases and five controls). Nearly all of the cases and controls in this job category were specifically identified as involved in the distribution, transport and movement of petroleum products, as opposed to the receipt and movement of crude oil.

## Discussion

The results of the analyses of exposure ratings are most consistent with the hypothesis of no effect on kidney cancer risk, or an effect too small for this study to measure with precision. This conclusion applies in particular to the results of the detailed analyses of the NALGD hydrocarbon category, in which *a priori* interest was greatest. After a recent consideration of all available research, the International Agency for Research on Cancer (*11*) described as "inadequate" both the epidemiologic evidence of carcinogenicity of gasoline and the evidence of an effect on kidney cancer risk of occupational exposures in petroleum refining. The results of the present study would not appear to warrant a reconsideration of those judgments.

Toxicologic studies indicate that the carcinogenicity of unleaded gasoline in male rats results from a nongenotoxic

**Table 7. Relative risks for longest-held jobs.**

| Job category | Cases | Controls | Relative risk | 95% CI |
|---|---|---|---|---|
| Administration and services | 23 | 97 | 1.00 | |
| Receipt, storage and movements | 9 | 15 | 2.49 | 0.95–6.56 |
| Laborer | 24 | 53 | 1.94 | 0.96–3.92 |
| Operator | 17 | 90 | 0.73 | 0.36–1.48 |
| Pipefitter | 4 | 49 | 0.33 | 0.10–1.05 |
| Machinist | 3 | 21 | 0.53 | 0.13–2.13 |
| Maintenance | 17 | 76 | 0.94 | 0.46–1.92 |
| Unit cleaner | 3 | 5 | 2.28 | 0.53–9.93 |

mechanism of tumor promotion due to chronic, reversible renal toxicity from long-term exposure to the $C_6+$ isoalkanes and certain other hydrocarbons and the consequent proliferation of the cells of the proximal renal tubule. Exposure of rat kidney cells to $C_6+$ isoalkanes stimulates replicative DNA synthesis but not unscheduled DNA synthesis (*41*). Whereas unscheduled DNA synthesis indicates repair subsequent to genotoxic insult, replicative DNA synthesis is characteristic of proliferative response to injury or necrosis. Thus, it has been suggested that "unleaded gasoline has little, if any, ability to initiate tumorigenesis in the kidney but, rather, may promote the development of spontaneously initiated tumors by mechanisms related to cell turnover" (*41*). A recent study showed a strong effect on renal cell tumor incidence when male Fischer 344 rats were exposed by inhalation to *N*-ethyl-*N*-hydroxyethylnitrosamine (a potent initiator) followed by exposure to unleaded gasoline or 2,2,4-trimethylpentane (i.e., iso-octane) and no such effect when the exposure sequence was reversed (*3*).

If a similar mechanism were operating in humans, one would expect to find associations between NALGD exposures and kidney cancer risk among older employees, after long-term exposure, and in relation to exposures that occurred relatively close in time to diagnosis. In the present study, strong associations were not present in the highest categories of cumulative exposure, in exposure periods close in time to the kidney cancer occurrence, or in the highest categories of age at diagnosis. Nevertheless, an association (RR = 2.5) did seem to be present between NALGD exposure and kidney cancer among employees in the oldest category of age at hire (≥ 35 years). On average, the exposures of these employees would have been sustained at older ages than the exposures of the other cases and controls. Occupational exposures encountered by these persons before working at the refineries in our study are unknown. This solitary and statistically unstable result (CI 0.7–8.7) is the only finding from the exposure-rating analysis that is even moderately consistent with a discernible effect of NALGD hydrocarbons on kidney cancer risk.

Misclassification of exposure is worthy of consideration as a possible explanation for the absence of strong positive associations between kidney cancer and the exposure ratings in this study. The exposure assessment was neither quantitative nor based directly on measurements of hydrocarbons in the refinery environment. Thus, a substantial potential existed for exposure misclassification. Because the industrial hygienists were unaware of the case or control status of the jobs they were rating, the frequency of classification errors should not have differed between the cases and controls. Consequently, bias in the relative risk estimates from exposure misclassification would be expected to be toward the null value of 1.0, and substantial bias toward the null from nondifferential misclassification of exposure cannot be ruled out in this study.

Nevertheless, the exposure assessment was far more detailed than in the original cohort mortality studies from which the cases and controls were identified. In most of those studies, the assessment of exposure consisted solely of documenting that a person had worked for a petroleum company or in a refinery. The present study should have reduced the degree of exposure misclassification considerably in comparison with those studies. If there was a major effect on kidney cancer by a refinery exposure that is even modestly associated with any of the primary or secondary exposures we considered, larger relative risk estimates would have been expected than the ones our analysis produced.

Misclassification of disease is a potential problem in this study because of the sole reliance on death certificate information. Missed cases (i.e., low sensitivity) would not be expected to be a major problem because most of the kidney cancer patients in this study would have been expected to die a short time after diagnosis. In the Third National Cancer Survey, the median observed survival time was 2.2 years among white men age 35 years and older and diagnosed in the years 1960–1973 (*30*). (Observed and not relative survival times are the appropriate measures in this context, where the important information is how long the patients actually survived.) These data should be reasonably applicable to the cases in the present study, at least 88% of whom are white, 81% of whom are age 35 and older, and 55% of whom are estimated to have been diagnosed in the same calendar period, with 25% diagnosed in earlier years and 21% in later years. In any event, no bias is produced by a failure to identify all cases if the probability of missing them does not differ by exposure (*42*).

Bias from false-positive disease classification errors (i.e., low specificity) is a problem of greater potential importance. All 100 deaths for whom exposure information was available were assigned the International Classification of Diseases code 189.0, "primary malignant neoplasm of the kidney, except kidney pelvis" (*43*). After investigating 930 death certificates with the same code, Percy et al. (*44*) failed to find a hospital record of the diagnosis for only 65 of the deaths, for a false-positive rate of no greater than 7%. More recent data compiled by Devesa et al. (*45*), however, suggest that incidence-registry records would show about 15 of 100 deaths with the 189.0 code to have been renal pelvis cancers and that cell-type review would result in a reclassification of 3 of the 85 remaining cases to renal pelvis cancer as well. Thus, the total number of renal pelvis cancers would be 18.

To obtain an upper limit on the degree of bias from false-positive disease classification errors, we assumed that 30 of the 100 cases were renal pelvis cancers and that renal pelvis cancer is completely unassociated with exposure. Under these hypothetical conditions, the relative risk of 1.25 for NALGD hydrocarbon exposures within 10 years of diagnosis (Table 5) would change to 1.37 and the relative risk of 1.22 for NALGD hydrocarbon exposures 10–19 years before diagnosis (Table 5) would change to 1.32. These computations suggest minimal bias from disease misclassification.

Confounding also needs to be considered. In estimating the relative risks for refinery exposures, we found that controlling for race, Spanish surname, and the matching factors (refinery location and age) did not materially alter the results. Confounding by gender was prevented by restricting the study to men. We had no information on nonoccupational risk factors for kidney cancer other than age and gender. Only a risk factor that is common in refinery work, that is particularly common in the refinery jobs that confer little or no exposure, and that has a high relative risk of its own could have obscured a major effect of the exposures we examined. No such factor is known at the present time.

One might suspect upward confounding of the relative risks if the exposed groups had a higher prevalence of cigarette smoking (*46*) or obesity, which are risk factors for kidney cancer and for cancers of the renal pelvis and ureter (*47*). Furthermore, diuretic medications are associated with obesity by virtue of their use to treat hypertension, and these drugs have also been associated with renal cell cancer (*47*). Confounding by these factors would be expected to be greatest in the analyses of longest-held jobs (Table 6), where the reference category includes all the white-collar jobs. The relative risk for all blue-collar jobs combined is only 1.05, however, suggesting a negligible degree of confounding by factors related to job class.

Of the species studied to date in laboratory toxicology, only the male rat appears to be susceptible to the carcinogenic effects of gasoline hydrocarbons in the kidney and the associated nephrotoxicity. The $C_6+$ isoalkanes and certain other hydrocarbons are apparently metabolized to derivatives capable of binding to a urinary protein, $\alpha_{2u}$-globulin, that is specific to the male rat. The protein-metabolite complex tends to accumulate in the cells of the proximal tubule to an extent that disrupts normal cellular function and causes the cells to die (*4,5,48,49*). These reversible effects are not seen in mice, dogs, guinea pigs, monkeys and female rats, all of which lack $\alpha_{2u}$-globulin (*50*). Thus, one tenable explanation for our results is that humans are not susceptible to an effect that is peculiar to the male rat.

In contrast with the analysis of exposure ratings, the analysis of job titles and units for the longest-held jobs produced associations less inconsistent with a pronounced effect of refinery exposures on kidney cancer risk. Workers in some of the jobs that would be expected to entail the greatest hydrocarbon exposures – laborers, unit cleaners and workers in receipt, storage, and movements – appeared to be at increased risk. It is possible that in the bulk of jobs within refineries, especially the refinery unit operators and the diverse jobs in the maintenance crafts, the variations in exposure were all within a range that was too low to produce measurable increases in kidney cancer risk in a study of this size. The only sizable group with an elevated relative risk, the laborers, also was the most difficult to assess with respect to refinery exposures because of these employees' nonspecific duties and refinery locations. The other jobs with elevated relative risks – the unit cleaners and the receipt, storage and movements workers – were too few to permit a more detailed analysis. If these results reflect an effect of some refinery exposure on kidney cancer risk, it would have to be an exposure other than, and not strongly associated with, any of the 10 exposures we examined.

The hydrocarbon composition of the completely volatilized gasoline to which the rats were exposed was unlike the composition of the vapors encountered in most situations of human gasoline exposure. In particular, the $C_6+$ isoalkanes were proportionately more abundant in the rat bioassays. These compounds make up 30–35% of liquid gasoline, but only 10% of gasoline vapor under ordinary circumstances (*51–53*). Studies of occupational groups with greater exposures to hydrocarbons, especially the $C_6+$ isoalkanes, than the exposures encountered in petroleum refineries would be highly informative. For this reason, gasoline station attendants and other workers in receipt, storage and movements would constitute particularly important groups to study.

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