A Nested Case–Control Study of Kidney Cancer among Refinery/Petrochemical Workers

John F. Gamble, Eileen D. Pearlman, and Mark J. Nicolich

Exxon Biomedical Sciences, Inc., East Millstone, NJ 08875-2350 USA

A nested case–control study was designed to evaluate whether a nearly twofold excess of kidney cancer among workers at a refinery/petrochemical plant was associated with cumulative exposure to C_2–C_5 saturated, C_2–C_5 unsaturated, C_6–C_{10} aliphatic saturated, C_6–C_{10} aliphatic unsaturated, and C_6–C_{10} aromatic process streams. Nonoccupational risk factors were body mass index (BMI), blood pressure (both measured at about age 28), and smoking. There was no significant association with cumulative exposure or tenure as estimated by conditional logistic regression and adjusted for nonoccupational risk factors. Categorical analysis showed increased odds ratios only in the second (low) and fourth (high) quartiles compared to the first quartile reference group of lowest exposed workers, and a three-quarter–fold increased odds ratio for >32 years' tenure compared to the <25-year reference group. The number of cases was small with wide confidence intervals around estimate of risk, so the possibility of an exposure–response trend cannot be ruled out. Multivariate analysis identified overweight (high BMI; $p<0.01$) as the most important risk factor in this data set, followed by tenure and increased blood pressure. There was a weak association with current smoking, but not with pack-years smoked. The risk of kidney cancer for a nonsmoker with normal blood pressure but 25% overweight was increased about 2.6-fold (95% CI = 1.2–5.4). The risk of kidney cancer for a nonsmoker of normal weight with high blood pressure (e.g., 150/110), was increased about 4.5 (95% CI, 0.8–26). *Key words*: blood pressure, case–control study, kidney cancer, petrochemical workers, petroleum hydrocarbons, refinery workers, smoking. *Environ Health Perspect* 104:642–650 (1996)

Mortality studies of workers at a refinery and petrochemical plant have shown about a 55% kidney cancer excess (*1*) and a nearly twofold excess after 8 more years of follow-up (*2*). There is little evidence from cohort studies (with the possible exception of distribution workers) to suggest that workers in the petroleum industry are at increased risk of kidney cancer (*3,4*). However, there is also no strong evidence to the contrary. The evidence from case–control studies is contradictory. Nested case–control studies within petroleum worker cohorts show no apparent association with exposure (*5,6*). However, several population-based case–control studies show an increased risk of kidney cancer related to exposure to petroleum products (*7*). Overall, the studies of humans are inconclusive regarding potential risk.

Beginning in the early 1980s, there is an extensive body of experimental data showing that a wide variety of chemicals (primarily C_6–C_{10} saturated aliphatics) produce renal tumors in the male rat. The predominant hypothesis regarding the mechanism ($\alpha 2_\mu$-globulin nephropathy) (*8,9,10*) has been considered irrelevant in evaluating carcinogenicity to humans of petroleum hydrocarbons. A recent review points out inconsistencies in the hypothesis and suggests the possibility that these hydrocarbons may be carcinogenic in themselves (*11,12*). Experimental data are valuable for assessing the potential for human carcinogenicity by providing, or not providing, a biologically plausible mechanism. Experimental data appear to support the evaluation of the Environmental Protection Agency (*13*) that the response of male rats to these chemicals is probably not relevant to humans. There is not at present a plausible mechanism to explain why there might be an association between exposure to petroleum products and kidney cancer.

To further test the hypothesis that hydrocarbons cause kidney cancer, we selected the refinery/petrochemical plant cohort studied by Shallenberger et al. (*2*) to conduct a nested case–control study. The major objectives of the study were to estimate the relative risk of cumulative exposure to the following process streams: C_2–C_5 saturated hydrocarbons, C_2–C_5 unsaturated hydrocarbons, C_6–C_{10} aliphatic saturated hydrocarbons, C_6–C_{10} aliphatic unsaturated hydrocarbons, and C_6–C_{10} aromatics.

Although the etiology of kidney cancer is little understood, there are several nonoccupational risk factors consistently associated with kidney cancer and for which data in this study are available. The odds ratios for obesity (generally measured as body mass index, or BMI) in six studies ranged from 1.2 to 3.3 (*14–20*). One study showed trends for the risk in males to increase as BMI increased, with greater than a twofold increased risk in the fourth quartile compared to first quartile for three measures of BMI: at age 20, most recent BMI, and highest BMI (*19,20*). Kadamani et al. (*21*) suggested there was a positive interaction between high BMI and hydrocarbon exposure.

The odds ratios associated with high blood pressure ranged from 1.5 to 2.9 in three of four case–control studies (*15,16,22*), and was below 1.0 in the fourth (*23*). Raynor et al. (*24*) found that only kidney cancer cases (out of 10 other sites) had systolic blood pressure values above the average of the total cohort (162 mm Hg versus 134 mm Hg).

There are 11 case–control studies and 4 prospective studies that evaluated the risk of kidney cancer by a quantitative measure of cigarettes smoked. Ten of the 11 case–control studies had odds ratios ranging from 1.3 to 4.7 for the heaviest smoking categories. The risk ratios in the four prospective studies ranged from 1.2 to 3.0. Thus, there was a consistent pattern showing smokers at increased risk of kidney cancer (*14–17,19,20,23,25–33*).

Secondary objectives in this study were to evaluate the risks that obesity (measured as BMI), blood pressure, and smoking pose for kidney cancer in this study population and to control for them while evaluating hydrocarbon exposure.

Methods

Definition of Cases and Controls

All cases and controls were part of the cohort studied by Shallenberger et al. (*2*), with at least 1 month of service at the refinery and chemical plant sites between 1 January 1970 and 31 December 1992. Current employees and employees retired before 1970 and still

Address correspondence to J. F. Gamble, Exxon Biomedical Sciences, Inc., Mettlers Road, CN 2350, East Millstone, NJ 08875-2350 USA.

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alive as of 1 January 1970 are included. Eligible cohort members were determined from company personnel and payroll records. Vital status and death certificates were obtained from company files and from states where decedents were identified through the National Death Index and the Social Security Administration. Follow-up was through 1990. Cause of death was coded by a trained nosologist according to the eighth revision of the International Classification of Diseases.

Cases were defined as anyone diagnosed with renal cell carcinoma or renal cell adenocarcinoma (ICD8 189; hereafter referred to as kidney cancer). Confirmation of kidney cancer is from the death certificate (either primary or secondary cause of death) or from pathology or bioassay reports from the company tumor registry. Date of diagnosis or date of death were determined from the death certificate or tumor registry report and were used to estimate time at risk. There were 32 cases with only date of death and this was the time used to estimate latency; 5 cases were not dead, for a total of 37 cases.

Four controls per case were selected at random from the set of persons in the cohort who were at risk when the case was at risk, and frequency matched on sex (all males), race, date of birth (DOB) (±1 year), date of hire (DOH) (±3 years), and at-risk status (control must be alive and free of disease at the date of diagnosis or date of death of the cases.) A control also had to have in the records a work history to be eligible. A control could only be selected once and could not be a control for more than one case. The work history of the controls was stopped at the date of death or date of diagnosis of the case. Out of a total cohort of 9894, there were 2473 eligible controls, with a range of 6–253 eligible controls per case.

Abstraction of Records

Information from questionnaires and clinical medical forms were abstracted from each employee's personnel file without knowledge of case or control status. Height, weight, blood pressure, and cholesterol were recorded when available from initial exam, and for the years closest to ages 40 and 55. Information on tobacco and alcohol use were recorded for initial and last entries and when there were any changes in between. Any reports on history (such as whether parents had kidney cancer, whether subjects had kidney stones, cysts, and exposure to X-rays) were also recorded from the physicians' reports. Since only weight, height, blood pressure, and smoking history were systematically recorded, these were the only demographic data used in the analyses.

All sources were used to estimate an average tobacco consumption. For cigarette smokers, an average of cigarettes smoked per day and total pack-years (packs smoked/day × years smoked) were calculated. The major sources of smoking history were a survey conducted in 1959, annuitant surveys in 1986 and 1991, and physicians' notes. Four cases and 10 controls had no smoking history.

Exposure History

There are several sources of work history data. Jobs held before 1977–1978 were summarized from personnel records and include all unique job locations. From 1978 to 1979, jobs had been computerized on an annual basis, and after 1988 on a monthly basis. For controls, the work history ended at the date of diagnosis or death of the case, whichever came first. For cases, the work history ended at either the date of termination or date of death (or diagnosis), whichever came first.

A four-step process was used by an industrial hygienist to rate the relative potential for exposure for each job title and job department/location combination. A "high" rating indicates a greater potential for significant exposure compared to ratings of "medium" or "low": 1) rate each job title: L = background level, office work only; ML = minimal exposure to fugitive emissions only, time is spent in the plant but no hands-on work, personnel loaned to other locations; MH = plant jobs but primarily in control rooms or in activities where exposure is intermittent and/or less intense than the high category; H = primary activities are in the plant with the highest potential for exposure (e.g., assistant operators, laborers, certain maintenance positions); 2) rate each job department/location for each process stream: L = unlikely to be present or present at low levels as a contaminant or extreme end of the process or product stream; M = present as part of process stream but not as a major constituent; H = major or primary component of the process feed/product stream; 3) develop an exposure matrix of job title ratings and job department/location ratings and assign numerical values: H/H = 4; H/MH and MH/MH = 3; ML/ML = 2; and H/L, MH/L, ML/L, and L/L = 1; 4) apply the matrix to each combination for each stream.

The primary factor determining the level of exposure was the job title. The primary determinant of the process stream or hydrocarbon stream was the department or location. A low rating in either category automatically resulted in a low rating for the combination.

Mechanical-related jobs were the most problematic for exposure scoring. It was not always clear whether maintenance personnel rotated through various locations or whether in the past they were assigned long term to specific process areas/units. Before 1966 this function made no distinction between refinery and chemical plant operations. Use of individual job histories helped in the identification of particular locations and process stream exposures. Most mechanical locations were rated high exposure, except for construction and/or planning, which were rated medium exposure.

There were two major time periods when significant changes occurred. The first was in the early 1940s with the implementation of a process engineering staff. This led to better designs and implementation of process controls. The second major period was the early 1970s with the advent of computerized controls, environmental regulation, and upgrading of job classifications. This resulted in better exposure control as well as the addition/elimination/change of job titles and tasks. The late 1960s/early 1970s also saw major changes in pumps and compressors: packing was replaced with mechanical seals and reciprocating equipment was replaced with centrifugal equipment. All of this led to a decrease in leakage and maintenance.

Another aspect of changes over time is the introduction/elimination of specific process units. As units change, the types and relative degree of exposure will change. This may also lead to changes in task activities and subsequent exposures of a particular job title. However, there was not enough historical information to estimate the magnitude of any change. The historical changes were, therefore, assumed to affect absolute exposure levels but not relative exposures between jobs. Cases and controls should be equally affected by these changes because they were matched on DOH.

Primary process stream composition is relatively consistent and traceable over time. The hypothesis being tested relates to petroleum hydrocarbons. Five primary process streams were identified, based on process operations and the ability to differentiate between streams at the various process units. The five streams identified were C_2–C_5 saturated (alkanes/paraffins, e.g., propane); C_2–C_5 unsaturated (alkenes/olefins, e.g., propene, 1,3-butadiene); C_6–C_{10} aliphatic saturated (paraffins/cycloparaffins, e.g., octane, cyclohexane); C_6–C_{10} aliphatic unsaturated hydrocarbons (olefins/diolefins, e.g., octene, decahydronaphthalene or decalin); and C_6–C_{10} aromatics (e.g., benzene, toluene).

Process streams in the refinery were considered to consist primarily of saturated

streams. Process streams in the chemical plant were considered to be primarily unsaturated or aromatic streams. A major exception was steam cracking units in the chemical plant where saturated refining feed stocks were used to generate unsaturated streams for downstream chemical plant feed stocks.

Exposure Classification

The characterization of exposure–response relationships is an objective of epidemiologic investigation and is a major criterion by which to evaluate causality. It was the primary purpose of this study to evaluate exposure–response relationships using hydrocarbon streams as the major exposure variable. Because the effect is a chronic one, cumulative exposure received over time is considered the most relevant estimate of exposure.

Cumulative exposure in this study is defined as score-years. Score-years is the summation of job exposure rating × tenure in that job. For example, score-years for an individual exposure to aromatics is calculated as follows: job title/locations ratings for helper/mechanic and foreman/mechanic are 4 and 2, respectively. If a person worked 8 and 15 years in each job, their score-years is $\Sigma(4\times8)+(2\times15)=62$, and tenure = 23 years.

Tenure or employment duration is a surrogate marker of total exposure. Tenure can be a reliable surrogate when there is one predominant hazardous exposure and when the following conditions are met (*34*): relatively constant concentrations throughout the plant, relatively constant concentrations over time, assignment to jobs with high and low exposure concentrations is unrelated to tenure, and nonoccupational risk factors do not vary according to tenure.

In this study population, probably none of the conditions are met with consistency. There is not a constant concentration throughout the plant, and persons with greater seniority and training tend to move into jobs with decreasing intensity of exposure. The condition of a relatively constant concentration is not met in the total cohort, but matching cases and controls on DOH makes this condition less relevant. Nonoccupational risk factors are indirectly related to tenure in that increasing weight and higher blood pressure tend to increase with age, as does increasing tenure. When there are multiple potentially hazardous exposures (e.g., process streams, possibly asbestos), analysis of tenure effects has a nonspecific interpretation.

Misclassification of exposure is less likely when intensity is included in estimates of exposure. Cumulative exposure is preferred over tenure because it attempts to take into account varying concentrations throughout the plant, job assignment, and multiple exposures.

Different jobs have different intensities of exposure associated with them, but for tenure, all jobs assume a similar intensity. The ratio of score-years to tenure indicates a range of values from 1/1 (lowest-exposed job) to 4/1 (highest-exposed job).

Statistical Analysis

The odds ratios were estimated based on both a continuous score and a grouped (discrete) score. For example, for the continuous analysis, the observed BMI was the variable, and for the discrete analysis, the BMI scores were categorized into four classes of approximately equal size (>21, 21–23, 23–25, and ≥25). For the discrete case, the odds ratio is the ratio of the odds for a given class relative to the base (reference) class. For the continuous score, the odds ratio is the change in the ratio of the odds when the risk variable is increased by one unit. The advantage of the continuous method is that it does not depend on the groupings chosen for the classes; the disadvantage is that it assumes the log of the odds ratio is a straight line function of the risk factor. Tables 2–6 present the odds ratios for the grouped and continuous analysis, each with and without an adjustment for lifestyle factors.

Both unadjusted and adjusted coefficients for trend are calculated. The unadjusted coefficient has only a single variable in the conditional logistic regression. The adjusted coefficient represents the effect of × adjusted for the effects of the other variables. For the three nonoccupational risk factors, the adjustment is only for the other two nonoccupational risk factors and without consideration of workplace exposure variables. For the exposure variables (tenure, score-years), the adjusted exposure coefficient adjusts for the effects of BMI, blood pressure, and pack-years smoked. The three nonoccupational risk factors included in these analyses are 1) BMI as a measure of obesity = [pounds/(height in inches)^2] × 703.1; 2) mean arterial pressure (MAP) as a measure of blood pressure = (systolic BP − diastolic BP)/3 + diastolic BP; and 3) smoking: pack-years smoked = Σ(packs of cigarettes smoked/day) (years smoked); nonsmokers, never smoked cigarettes; ex-smokers, stopped smoking >1 year before end of at-risk status; smokers, >100 cigarettes in a lifetime. Pack-years is the variable used to estimate adjusted ORs and coefficients for the other variables, but grouped analyses by smoking category is also provided.

Results

Table 1 summarizes the characteristics of the 37 kidney cancer cases and 148 controls. Age and year of hire were quite similar between cases and controls, with DOB ranging from 1893 to 1944 and DOH from 1916 to 1980. The number of pack-years smoked by cases and controls was similar, but the proportion of ever-smokers was dissimilar. About one-fourth of the cases and controls were never-smokers. Among controls, the proportion of smokers and former smokers was about 50/50, but among cases was about 3/1. On average, the

Table 1. Characteristics of kidney cancer cases and controls

Characteristic	Case	Control
n	37	148
Mean year of birth (range)	1913.4 (1894–1944)	1913.5 (1893–1943)
Mean year of hire (range)	1941.4 (1919–1979)	1941.05 (1916–1980)
Nonsmokers, *n* (%)[a]	9 (27)	32 (23)
Former smokers, *n* (%)	6 (18)	55 (40)
Mean pack-years (SD)[b]	18.3 (14.1)	15.2 (13.4)
Smokers, *n* (%)	18 (55)	52 (37)
Mean pack-years (SD)	25.7 (17.2)	26.5 (16.1)
Mean tenure (SD; range)	30.7 (8.9; 1.4–50)	29.7 (8.5; 0.1–44)
Cumulative exposure scores, mean (SD; range)		
C_2–C_5 saturated	96.92 (36.1; 15–165)	88.58 (34.1; 0.5–154)
C_2–C_5 unsaturated	90.40 (33.7; 15–162)	84.44 (34.0; 0.5–154)
C_6–C_{10} aliphatic saturated	93.25 (38.0; 15–162)	86.64 (34.3; 0.5–154)
C_6–C_{10} aliphatic unsaturated	87.70 (34.75; 15–162)	82.99 (33.44; 0.5–154)
C_6–C_{10} aromatics	90.19 (37.2; 15–162)	84.27 (34.5; 0.5–162)
Body mass index, initial exam, mean (SD; range)[c]	24.5 (3.0; 18.6–31.4)	22.9 (2.8; 16.6–35.3)
Mean arterial pressure, initial exam, mean (SD)[d]	97.5 (7.8)	94.5 (7.6)
Blood pressure, initial exam, systolic/diastolic (SD)	129/82 (10.6/8.3)	125/79 (10.6/8.1)
Age at initial exam, mean years (SD)[e]	28.6 (6.7)	27.6 (6.5)

[a] *n* = 33 cases and 139 controls with known smoking history.
[b] Pack-years for 52 controls.
[c] Cases, *n* = 34; control, *n* = 141.
[d] Control, *n* = 145.
[e] Control, *n* = 145.

cases tended to have slightly increased BMI, blood pressure, and cumulative exposure scores compared to controls.

Tables 2–4 summarize the data showing the association of BMI, MAP, and smoking with risk of kidney cancer. Both adjusted and unadjusted risk ratios increase with increasing BMIs above the third quartile category. The adjusted regression coefficient indicates the risk ratio increases 0.17 for each unit increase in BMI (Table 2). That is, compared to a nonsmoker with normal blood pressure (120/80 with a MAP of 93.3) and an ideal BMI of 22.1 (*35*), a person 125% overweight (BMI = 27.6) has a calculated risk ratio of 2.58 (95% CI, 1.20–5.41).

The risk of kidney cancer tends to increase as arterial blood pressure increases, both with and without adjustment for BMI and smoking (Table 3). That is, a nonsmoker with ideal BMI but with hypertension (blood pressure = 150/110, MAP = 123.3) has a risk ratio of 4.48 (95% CI, 0.77–26.2) compared to a person with normal blood pressure (120/80). Although the point estimate shows a nearly fivefold increased risk, the 95% CI is quite wide.

There is no strong association of kidney cancer with smoking in this study population, either by smoking category or by pack-years smoked (Table 4). The calculated risk ratio is 1.32 (95% CI, 0.44–4.0) for a smoker with 40 pack-years but normal blood pressure and ideal BMI. Nevertheless, the pack-years variable is included (as well as BMI and MAP) in the calculation of adjusted values estimating the association with cumulative exposure.

When all three of the nonoccupational potential risk factors (high BMI, hypertension, heavy smoker) are present, the calculated risk ratio based on the equation ln OR = 0.172 (BMI) + 0.052 (MAP) + 0.007 (pack-years) is 14.4 with a 95% CI of 0.44–605.

Both adjusted and nonadjusted odds ratios tend to increase as tenure increases (Table 5). The odds ratios are increased three- and fourfold for the two groups with the longest tenure compared to the reference group with <25 years' tenure. The trend is close to significance in the conditional logistic regression model.

Table 6 summarizes the data showing the association of cumulative exposure with the risk of kidney cancer. None of the process streams show a statistically significant trend for the risk to increase as estimated cumulative exposure increases. The patterns in the grouped process stream data are similar, with the second and fourth quartiles showing higher risk ratios than the third quartile, which has point estimates around 1. That is, the risk ratio does not show a linear increase as cumulative exposure increases. The adjusted risk ratios are generally larger and have wider confidence intervals than unadjusted risk ratios. When a linear increase is assumed and the logistic regression models are used to estimate risk ratios (high exposed with a cumulative exposure score of 140 compared to low exposure with a cumulative exposure score of 30), the adjusted odds ratios and 95% CIs are as follows: stream 1, C_2–C_5 saturated, 4.18 (0.60–29.1); stream 2, C_2–C_5 unsaturated, 4.18 (0.74–23.5); stream 3, C_6–C_{10} aliphatic saturated, 3.74 (0.54–26.1); stream 4, C_6–C_{10} aliphatic unsaturated, 3.35 (0.48–23.3); stream 5, C_6–C_{10} aromatic, 2.41 (0.35–16.8).

The categorical analysis suggested a nonmonotonic increase, although the odds

Table 2. Odds ratios (OR) and coefficients from logistic regression analyses of the association of kidney cancer and body mass index (BMI)[a]

BMI	Cases	Controls	Adjusted[b] OR	Adjusted[b] 95% CI	Unadjusted OR	Unadjusted 95% CI
≥25	13	28	3.29	0.93–11.62	3.18	1.00–10.13
23–25	10	30	2.47	0.68–8.98	2.41	0.73–8.02
21–23	6	44	0.93	0.22–3.84	1.16	0.31–4.34
<21	5	39	1.0		1.0	

[a]Coefficient (SE) for trend in BMI adjusted for mean arterial pressure (MAP) and pack-years: 0.17 (0.07), $p<0.01$; coefficient (SE) for trend in BMI, unadjusted: 0.15 (0.06), $p<0.02$. Adjusted logistic regression equation: ln OR = 0.172 (BMI) + 0.052 (MAP) + 0.007 (pack-years).
[b]Adjusted for MAP and pack-years smoked.

Table 3. Odds ratios (OR) and coefficients from logistic regression analyses of the association of kidney cancer and mean arterial pressure (MAP)[a]

MAP	Cases	Controls	Adjusted[b] OR	Adjusted[b] 95% CI	Unadjusted OR	Unadjusted 95% CI
≥103	10	20	5.76	0.94–35.28	4.47	1.06–18.58
88–103	24	100	3.27	0.58–18.65	2.01	0.55–7.32
<88	3	25	1.0		1.0	

[a]Coefficient (SE) for trend in MAP adjusted for body mass index (BMI) and pack-years: 0.05 (0.03), $p<0.08$; coefficient (SE) for trend in MAP, unadjusted: 0.06 (0.03), $p<0.03$. See Table 2 for adjusted logistic regression with all nonoccupational variables included.
[b]Adjusted for BMI and pack-years smoked.

Table 4. Odds ratios (OR) and coefficients from logistic regression analyses of the association of kidney cancer and smoking cigarettes[a]

Smoking category	Cases	Controls	Adjusted[b] OR	Adjusted[b] 95% CI	Unadjusted OR	Unadjusted 95% CI
Smoker	18	52	1.36	0.44–4.19	1.21	0.44–3.35
Ex-smoker	6	55	0.58	0.17–1.97	0.37	0.12–1.18
Nonsmoker	9	32	1.0		1.0	

[a]Coefficient (SE) for trend in pack-years adjusted for body mass index (BMI) and mean arterial pressure (MAP): 0.007 (0.014), $p<0.62$; coefficient (SE) for trend in pack-years, unadjusted: 0.005 (0.012), $p<0.66$. See Table 2 for adjusted logistic regression using pack-years as the smoking variable. Adjusted logistic regression equation: ln OR = 0.139 (BMI) + 0.049 (MAP) – 0.552 (ex-smoker) + 0.309 (smoker).
[b]Adjusted for BMI and MAP.

Table 5. Odds ratios (OR) and coefficients from logistic regression analyses of the association of kidney cancer and tenure (years employed)[a]

Tenure (years)	Cases	Controls	Adjusted[b] OR	Adjusted[b] 95% CI	Unadjusted OR	Unadjusted 95% CI
≥38	9	27	4.08	0.24–68.72	6.68	0.47–94.74
32–38	9	39	3.26	0.27–39.72	3.01	0.27–33.47
25–32	9	39	1.34	0.23–7.77	1.37	0.29–6.44
<25	10	43	1.0		1.0	

[a]Coefficient (SE) for trend in tenure adjusted for body mass index (BMI), mean arterial pressure (MAP), and pack-years: 0.16 (0.09), $p<0.07$; coefficient (SE) for trend in tenure, unadjusted: 0.16 (0.08) $p<0.04$. Adjusted logistic regression equation for tenure: ln OR = 0.160 (BMI) + 0.055 (MAP) + 0.006 (pack-years) + 0.16 (tenure).
[b]Adjusted for BMI, MAP, and pack-years smoked.

Table 6. Summary of odds ratios (OR) and coefficients from logistic regression analyses of the association of kidney cancer and exposure to petroleum hydrocarbon measured as cumulative exposure (score-years)

Process stream	Adjusted OR (95% CI) by quartile of cumulative exposure				Trend coefficients (SE)	
	<65	65–90	90–115	≥115	Adjusted	Unadjusted
C_2–C_5 saturated	1	4.85 (1.0–23.6)	1.34 (0.25–7.1)	4.94 (0.88– 27.4)	0.013 (0.009)	0.012 (0.007)
C_2–C_5 unsaturated	1	4.28 (1.05–17.5)	0.52 (0.07–3.7)	5.09 (0.79–32.8)	0.013 (0.008)	0.009 (0.007)
C_6–C_{10} aliphatic saturated	1	4.45 (0.94–21.0)	0.92 (0.17–5.0)	4.17 (0.73–23.7)	0.012 (0.009)	0.010 (0.007)
C_6–C_{10} aliphatic unsaturated	1	2.86 (0.71–11.5)	0.56 (0.10–3.3)	3.93 (0.65–23.7)	0.011 (0.009)	0.007 (0.007)
C_6–C_{10} aromatic	1	2.97 (0.72–12.2)	1.01 (0.21–4.9)	3.73 (0.66–20.9)	0.008 (0.009)	0.009 (0.007)

ratio for each quartile was generally not significant and sometimes <1. The logistic regression did not show a monotonic response. Three possible reasons no monotonic increase was shown are: there is no relationship with exposure, there is no monotonic increase in risk with increasing exposure, and there is insufficient power to detect an effect.

Regression diagnostics showed no unusual behavior or undue influence of data points to suggest an exposure–response trend. The quartile analysis did not appear to be monotonic, so the lack of statistical power may not be a sufficient answer. However, the point estimates of the odds ratios are elevated but unstable, as shown by the very wide confidence intervals.

Based on this reasoning, the evidence is most suggestive of no relationship. Table 7 summarizes the adjusted and unadjusted odds ratios for all risk factors, for the highest quartile.

Figure 1 summarizes the cumulative frequency of renal cancer death by time since hire and time since terminating work. Latency since time of hire ranged from 24 to 62 years. Latency since termination was less than 22 years. When plotted on a cumulative log-normal plot, latency since termination does not approximate a log-normal distribution, whereas latency since hire does appear to show a log-normal distribution with a median of about 45 years (data not shown).

Table 7. Summary of adjusted and unadjusted odds ratios (OR) from occupational and nonoccupational variables[a]

Variable	Unadjusted OR	Adjusted OR	Unadjusted *p*-value	Adjusted *p*-value
BMI ≥25	3.18	3.29	<0.02	<0.01
MAP ≥103	4.47	5.76	<0.03	<0.08
Smoking	1.21	1.36	<0.66	<0.62
Tenure ≥38 years	6.68	4.08	<0.04	<0.07
C_2–C_5 saturated ≥115	3.08	4.94	<0.10	<0.15
C_2–C_5 unsaturated ≥115	2.55	5.09	<0.22	<0.14
C_6–C_{10} aliphatic saturated ≥115	2.46	4.17	<0.18	<0.17
C_6–C_{10} aliphatic unsaturated ≥115	2.23	3.93	<0.32	<0.22
C_6–C_{10} aromatic ≥115	3.25	3.73	<0.23	<0.32

Abbreviations: BMI, body mass index; MAP, mean arterial pressure.
[a]The adjusted analyses for BMI, MAP, and smoking contain the other two variables.
For the remaining dependent variables, all the adjusted analyses contain BMI, MAP, and smoking. The unadjusted analyses were adjusted only for age.

Discussion

This nested case–control study was composed of 37 male workers with kidney cancer and 148 controls matched on DOB, DOH, gender, and race. The *a priori* questions were the associations of kidney cancer with cumulative hydrocarbon exposure at work and three individual risk factors. In these workers there was a significant risk associated with BMI. The risk increased linearly with BMI and was increased about 2.6-fold for 125% overweight compared to normal BMI. There was a tendency for the kidney cancer cases to have higher blood pressure, longer tenure, and higher exposure to hydrocarbons (estimated as cumulative exposure to C_2–C_5 saturated, C_2–C_5 unsaturated, C_6–C_{10} aliphatic saturated, C_6–C_{10} aliphatic unsaturated, and C_6–C_{10} aromatics). The trend was linear for BMI, blood pressure, and tenure, but was not linear for the estimates of cumulative hydrocarbon exposure; none was statistically significant except the trend for BMI. Where no statistical significance was shown, the role of chance could not be discounted, as the confidence intervals around the odds ratios were quite wide. There was no association of kidney cancer with either smoking category or pack-years smoked.

Does this study test the light-hydrocarbon nephropathy hypothesis developed from the toxicology studies? The components of gasoline primarily responsible for the nephrotoxic activity of unleaded gasoline in the male rat are the branched saturated alkanes, C_6–C_9 (stream 3). These are light alkylate naphthas in the 145–280°F boiling range (*36*) and include 2-methylpentane, 2-methylhexane, 2,3-dimethylbutane, 2,2,4-trimethylpentane, and 2,2,5-trimethylhexane. Normal alkanes, alkenes, olefins, and aromatic compounds (i.e., process streams 1, 2, 4, and 5, respectively) did not show nephrotoxic effects. Thus, if the $\alpha 2_\mu$-globulin rat model hypothesis is relevant to humans, process stream 3 would be the most relevant exposure in this study.

Because of the high correlation (r >0.9 for any pair) between process streams, the observations are not independent and there is little difference in their exposure–response relationships in this study. Therefore, this part of the hypothesis cannot be tested in this data set. The "see-saw" nonlinear relationship of kidney cancer and process stream exposure is not characteristic of an exposure– response trend and contrary to what is expected when there is a causal association.

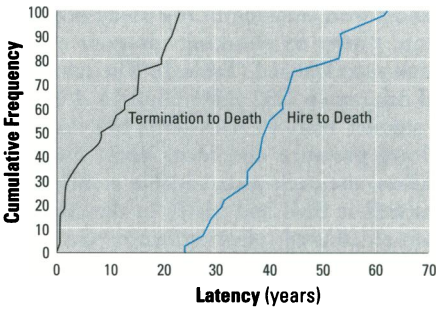

Figure 1. Cumulative frequency for latency.

Bias

Systematic errors are of particular concern in case–control studies. Potential biases due to selective recall and misclassification of disease and exposure are considered below.

A common problem in population-based case–control studies is recall bias. This occurs when cases remember more than controls about significant events or exposures that occurred in their past. As records were recorded prior to disease status, the possibility of recall bias is excluded.

Misclassification of kidney cancer is considered to be low. Percy et al. (*37*), examined 984 cases of kidney cancer to determine agreement between hospital and death certificate diagnoses. The detection rate (proportion of hospital diagnoses reflected as cause of death on death certificates) for kidney cancer was 87.9% and the confirmation rate (proportion of death certificate diagnoses confirmed by hospital diagnoses) was 93%. Thus, there were about 7% false positives with respect to kidney cancer as the underlying cause of death, or perhaps two misdiagnoses of the cases in this study.

The male rat model suggests an exposure–response curve showing a continous increase in tumors above the threshold exposure. The point estimates of the odds ratios in this epidemiologic study do not increase in a linear fashion, as the point estimates relative to the first quartile are elevated for the second and fourth quartiles, but the third quartile is generally <1. However, the confidence intervals are quite wide, so that drawing a curve through the lower confidence interval of the medium-low exposure category and through the upper confidence interval of the medium-high exposure category would result in the familiar exposure–response curve, i.e., continual increase response as exposure increases. The regression analysis suggests this is an unlikely event (about 1 chance in 6). The point estimates would move in the direction of a linear increase if there was nondifferential misclassification between medium-high to high exposure categories and medium-low to medium-high exposure categories.

On the other hand, these curves are similar in shape to those describing the relationship with aromatics in the Poole et al. (*5*) study of petroleum refinery workers, except their odds ratios are <2 in the medium-low and high categories, rather than the three- to fivefold increases seen in this study.

Thus, the point estimate for the odds of exposure are not like an exposure–response relationship, but the point estimates are unstable with very wide confidence intervals. More subjects are needed to more clearly define the shape of the curve.

Misclassification of exposure in case–control studies is a major concern as exposure–response relationships are a major measure of effect. For dichotomous exposures (exposure classified as yes or no), nondifferential misclassification tends to reduce risk ratios toward the null and decrease the power of statistical tests (*38*). Nondifferential misclassification occurs when the bias is independent of disease status or is random. In this study any misclassification of exposure is presumed to be nondifferential, as classification of exposure was made on the basis of job title/job location without knowledge of case or control status.

Marshall et al. (*39*) examined the potential effects of misclassifications on assessing exposure–response relationships, assuming misclassification only between adjacent exposure categories. They showed that if the pattern of errors is random, the bias will generally not mask an exposure–response trend. If the error rate is less than about 35%, the null hypothesis of no trend would be consistently rejected at the 5% level of significance for a sample size smaller than this study. A 50% misclassification rate would reduce a true odds ratio of 4 to an odds ratio between 2 and 3.

We have no way of determining if, or to what degree, misclassification may have occurred in this study. The blinded assessment of exposure intensity and the collection of work and medical history for both cases and controls from prerecorded personnel records suggest that any misclassifications are nondifferential. Given the apparent robustness suggested by Marshall et al. (*39*), bias is considered unlikely to significantly affect the exposure–response relationship shown in this study.

Selection bias could occur if kidney cancer retirees not dying before 1970 had nonrepresentative exposures. Ten of the 37 cases were retirees who were alive as of 1 January 1970.

Criteria for Causality

A number of criteria are regularly used in epidemiology to evaluate whether an association between an exposure and a disease is causal. Some of these criteria are considered in the context of the question posed in this study of whether hydrocarbon exposure increases the risk of kidney cancer.

The minimum period of time since DOH is 24 years among these cases, which should be sufficient time for the disease to develop if related to work exposure.

The presence of a trend of increasing risk with increasing exposure is strong evidence of a causal association. Risk tended to increase as tenure exceeded 30 years. Tenure is a surrogate and nonspecific measure of exposure and undoubtedly misclassifies exposure to process streams. Misclassification bias is considered less likely for estimates of cumulative exposure. However, the number of kidney cancer cases is relatively small, and the confidence intervals around both the slope of the exposure–response regression line and the odds ratios by exposure group are so wide that the possibility of a trend cannot be conclusively ruled out. Thus, the occurrence of an exposure–response trend is considered indeterminate.

Confounding by nonoccupational risk factors (BMI, MAP, smoking) is unlikely as they were adjusted for in the analysis, and are probably not related to exposure. There is potential confounding from asbestos exposure, where high exposure in asbestos-exposed cohorts showing a twofold or greater increased risk of lung cancer also show about a twofold increased risk of kidney cancer (*40,41*). We were not able to assess asbestos exposure, but it seems unlikely that the medium-low and high exposure categories of cases but not controls would be exposed to high enough levels of asbestos to increase the risk of kidney cancer. The risk of kidney cancer from asbestos exposure is also probably much less than the twofold risk observed in heavily exposed asbestos workers (*42*). Therefore, asbestos is not considered to be a likely confounder because differential exposure between cases and controls is unlikely, and the risk of kidney cancer from low-level exposure is probably too small to materially affect the odds ratios.

There are two other nested case–control studies within the petroleum industry. Both are of refinery workers (*5,6*) and do not show any apparent exposure–response trend. Poole et al. (*5*) identified 102 kidney cancer cases among five petroleum companies. There was no apparent increased risk associated with cumulative exposure to nonaromatic liquid gasoline distillates, aromatic hydrocarbons, and volatile hydrocarbons. There was about a twofold increased risk when the job held longest was laborer; jobs in receipt, storage, and movements; and unit cleaners. Wen (*6*) identified 22 kidney cancer cases in a Gulf oil refinery cohort. Odds ratios tended to decrease with increasing length of exposure to gasoline.

Occupational risk factors in population-based case–control studies are rarely suitable for establishing causality as exposure classification is generally inadequate because of too few exposed cases, exposure being too broadly defined and encompassing disparate jobs, industries, chemicals, and exposure–response usually being dichotomous. Population-based case–control studies provide suggestive evidence of a possible association of kidney cancer risk with various hydrocarbon-related jobs and industries including gasoline, kerosene, aviation fuel, petroleum refining and distribution, gasoline attendants, petroleum products, organic solvents, chemical manufacturing, and hydrocarbons (*3,7*). There are a number of other nonhydrocarbon-related job/industries that also show increased odds ratios. However, they have obscure, if

any, association with exposure to petroleum hydrocarbons and no known or suspected etiologic agent. These associations indicate the problem of multiple comparisons, i.e., if enough comparisons are made, something is bound to be significant.

Cohort studies of petroleum industry workers provide little evidence of possible increased risk, even when more highly exposed workers are analyzed separately (*3,4*). These cohort studies are often limited in evaluating risk and causality for several reasons, including exposure to multiple substances, inclusion of a proportion of workers with little or no exposure (which dilutes or obscures any work-related effect), some workers with too-short latency unless stratified by time since hire, and no evaluation of exposure–response trends.

None of the three available nested case–control studies directly addressing the question of whether petroleum hydrocarbons increase the risk of kidney cancer is clearly positive. The population-based case–control studies suggest there are a variety of chemicals and jobs that may be associated with increased risk of kidney cancer. The most specific substances identified are fuels (e.g., gasoline, kerosene, aviation fuel). Two cohort studies of distribution workers are consistent with the findings from the population-based case–control studies, but two are not, and the latter do not suggest an association with exposure.

The $\alpha 2_{\mu}$-globulin hydrocarbon hypothesis describes a possible mechanism whereby hydrocarbons might cause kidney tumors in the male rat. This hypothesis does not appear to be a plausible mechanism in humans (*9*).

Latent periods for a number of cancers show a log-normal distribution from time of exposure to the etiologic agent. Armenian and Lilienfeld (*43,44*) provided several examples of this relationship including thyroid cancer and childhood radiation exposure, leukemia following exposure to radiotherapy, intrauterine X-ray exposure, and radiation from the atomic bomb. Three examples were given where the onset of exposure was less precise; namely, lung cancer in asbestos workers and two instances of bladder cancer following occupational exposures to dyes. An exception to the log-normal distribution was noted for onset of acute lymphatic leukemia in children not exposed to intrauterine X-rays.

Similar distributions are seen for the incubation period of infectious diseases (*44*) and age of onset for genetic diseases (*45*). They suggest that observing a log-normal distribution of incubation periods in these diseases, as well as cancers caused by some environmental exposure, is suggestive that a specific etiologic agent initiates a chain of events that leads to the disease.

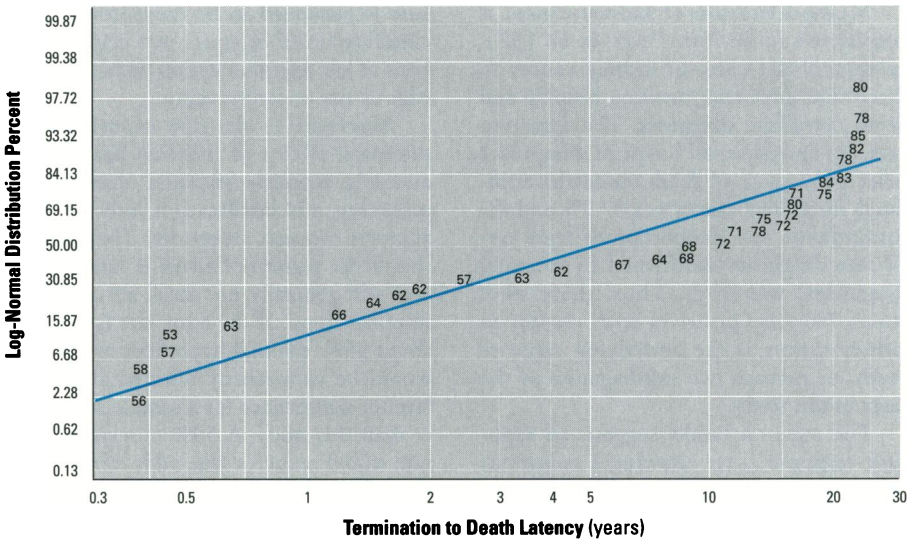

Figure 2. Cumulative log-normal plot for latency.

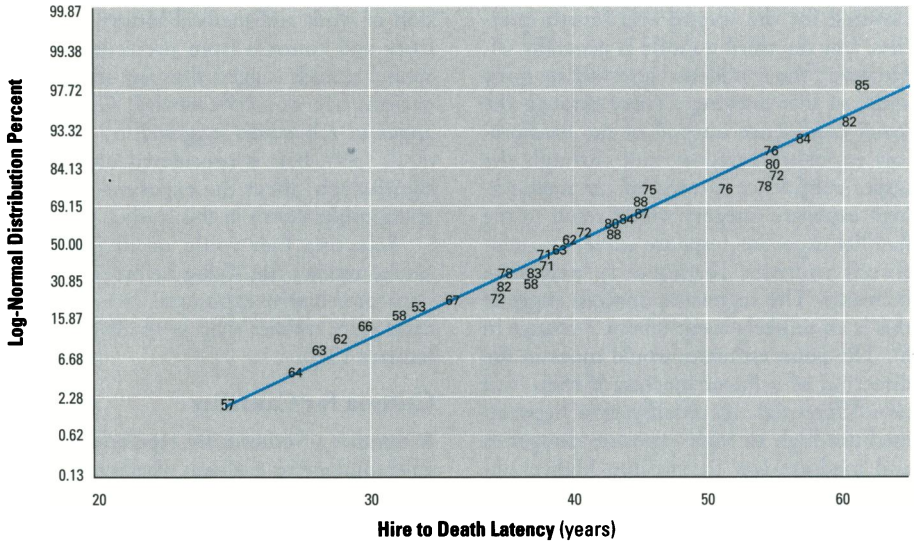

Figure 3. Cumulative log-normal plot for latency.

The study of the distribution of incubation periods may therefore be useful in determining the importance of a particular factor in causing a disease. The absence of a fit (as for termination of employment in this study; Fig. 2) may suggest the factor is not important. The presence of a fit (Fig. 3) is suggestive of an association.

The reasoning by analogy is somewhat like plausibility. If several different carcinogenic agents produce a log-normal latency distribution, then it is easier to accept the idea that the appearance of a latency log-normal distribution is associated with a common etiologic agent or exposure.

Is there a positive association that cannot be explained by bias, confounding, or chance? Misclassification bias was discussed and considered unlikely to obscure the presence of a trend. BMI, MAP, and smoking are three potentially confounding factors. These factors were included in the calculation of adjusted odds ratios and coefficients. Further, the controls were drawn from the same cohort as the cases, so neither bias nor confounding is considered to have any significant impact on the study results.

However, it is possible that no statistically significant association was observed because of the lack of power to detect an effect. For example, the adjusted odds ratio for a cumulative exposure of 100 score-years to stream 3 is 3.3 with the possibility that the "true" odds ratio is as low as 0.57 or as high as 19.4. The wide confidence intervals on the estimates of risk are a reason for concluding that this study has low power and therefore does not provide clear

Table 8. Summary of association of kidney cancer and body mass index among males in population-based case–control studies compared to this study

Reference	ORs (95% CI) by quartiles				Total number	
	Low	2nd Quartile	3rd Quartile	High	Cases	Controls
(22)[a]	1.0	1.01	1.76	1.16	129	256
(13)	1.0	0.9 (0.5–1.1)	0.8 (0.5–1.3)	1.3 (0.8–1.8)	310	426
(48)	1.0			2.0 (1.2–3.2)		
(14)	1.0	1.0 (0.4–2.4)	1.0 (0.5–2.4)	2.2 (1.0–4.9)	104	104
(16)	1.0	1.93 (1.12–3.77)	2.67 (1.49–5.94)	—	189	189
(18)	1.0	1.2 (0.7–2.1)	1.6 (0.9–2.9)	2.5 (1.4–4.6)	206	195
(20)[b]						
No hydrocarbon exposure	1.0	1.0	3.7	3.8	21	35
Low hydrocarbon exposure	1.0	1.12	4.24	0.71	29	35
Moderate hydrocarbon exposure	1.0	1.71	0.83	1.02	53	36
High hydrocarbon exposure	1.0	0.86	4.14	8.14	39	36
This study	1.0	0.93 (0.22–3.84)	2.47 (0.68–8.98)	3.29 (0.93–11.6)	34	141

ORs, odds ratios.
[a]Odds ratios calculated from the data.
[b]Odds ratios of quartiles 2–4 adjusted relative to quartile 1. The odds ratio of first quartile was 1.7, 4.2, and 1.4 for low, moderate, and high hydrocarbon exposure compared to 1st quartile of no hydrocarbon exposure.

evidence for or against an exposure–response relationship or causal association. The study included all the extant cases of kidney cancer in the study population. Hence it is not possible to increase the power of the study until we observe more cases in the study population.

Table 8 summarizes studies that have evaluated the association of kidney cancer with BMI among men, including the results of this study. Practically all of the studies show a trend for the risk to increase as the body weight increases. Wynder et al. (*23*) and McLaughlin et al. (*14*) showed an effect for overweight women but not for men. Goodman et al. (*17*) found a significant trend among both men and women that was somewhat more consistent among men.

The data from this study and from two earlier studies (*15,20*) suggest that a young male 120–130% above normal weight is at two- to threefold increased risk of kidney cancer. Asal et al. (*20*) performed a multivariate analysis and ranked the most important variables as assessed by stepwise regression as 1) recent weight (p = 0.0001), 2) petroleum work (p = 0.0006), and 3) hypertension (p = 0.04) as among the most important risk factors for kidney cancer. Smoking (p = 0.08) was ranked 11th. Thus, the study reported here is consistent with other studies suggesting that being overweight increases the risk of kidney cancer among men.

In this study, blood pressure (measured as mean arterial pressure) showed a trend of increasing risk with increasing MAP measured at initial exam. Grove et al. (*46*) found a significant association of blood pressure (10 mm Hg increase) with the incidence of kidney cancer (controlled for age and smoking) among men. After adjustment for blood pressure medication, however, the association was no longer significant. Age at which blood pressure readings were taken ranged from 46 to 68 years. Other case–control studies have not measured blood pressure directly, but categorized exposure as the presence or absence of hypertension, and sometimes adjusted for use of diuretics and hypertension drugs (*22,15,23,29*). Yu et al. (*15*) found that men with high blood pressure and taking diuretics had a slightly increased odds ratio of 1.2 (95% CI, 0.4–4.0) compared to those not taking a diuretic. Both Yu et al. (*15*) and McLaughlin et al. (*47*) found no association with diuretic use alone among men.

The findings of this study are consistent with those in the literature. However, in this study the blood pressure readings are for young men in good health and without the presence of potentially confounding health factors and medications present in older men. The observed trend is suggestive of a causal association but needs to be confirmed.

The association of cigarette smoking and risk of kidney cancer among males has been investigated in a number of case–control studies (*14,15,17,19,22,23,26,28,29,48*). In general, there was a trend for the odds ratios to increase as the level of smoking increased. However, the odds ratios even among the heaviest smokers were only moderately elevated (range of 1.27–2.2). Heavy smokers in this study fall in the lower part of this range. Three studies reported only ever-smokers, and the range was 1.0–2.24. The odds ratio was 1.36 for the study reported here.

These results suggest there is a weak association of kidney cancer among moderate to heavy smokers. The study reported here is consistent with that conclusion based on classification by smoking category. The lack of an association with pack-years may in part be due to the inclusion of former smokers. Most of the studies in the literature do not evaluate pack-years as a risk factor.

Conclusions

The primary objective of this study was to investigate the association of kidney cancer and hydrocarbon exposure using exposure–response as the measure of association. After controlling for weight, blood pressure, and pack-years smoked, there was no clear-cut exposure–response relationship with tenure or qualitative estimates of cumulative exposure. However, the number of kidney cancer cases is relatively small, and the confidence intervals around both the slope of the exposure–response regression line and the odds ratios by exposure group are so wide that the possibility of a trend cannot be ruled out.

The associations of kidney cancer with BMI and MAP are characteristics of a causal relationship, as the odds ratios increase in a linear fashion. Weight and blood pressure information was collected at the time of first employment or about the start of exposure, so the time sequence is appropriate. For BMI the risk is not observed until the person is overweight, which for men is a BMI >26.5 (*35*). Blood pressure and BMI in this study were measured on physical exam at a young age. Other studies have less specific measures of blood pressure and were obtained at times closer to the disease state. Increased blood pressure does appear to be a risk factor for kidney cancer, but there is a need for more precision in the estimated risk at specific blood pressure (and BMI) levels. Smoking, evaluated both as smoking category and by pack-years, does not show a strong association with kidney cancer.

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