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Epidemiologic Evidence for an Association Between Gasoline and Kidney Cancer

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A recent animal experiment suggests that gasoline exposure may be a cause of human kidney cancer. This is a literature review to see whether there is any epidemiologic support for these animal findings. Trends and geographic patterns in gasoline consumption and kidney cancer mortality are moderately supportive of a relationship, although this cannot be considered important evidence for a causal relationship. Most other ecological correlations are not supportive of a relationship. Eleven oil refinery populations and one population of petroleum products distribution workers have been studied. These studies taken as a group do not appear to support the notion of a relationship between gasoline exposure and kidney cancer. However, most were not designed or analyzed with this hypothesis in mind. An examination of these data which attempts to consider the ages of the populations studied provides some evidence of a small kidney cancer excess among older workers or among workers exposed for long periods. Because of the importance of gasoline and the potential for exposure by the public further study of exposed populations is needed.

A chronic inhalation study has shown that unleaded gasoline vapor caused kidney carcinomas and sarcomas in male rats with some evidence of a dose-response relationship (*1*). Also observed was an increase in liver masses and modules in female mice. Parallel experiments involving female rats and male mice were essentially negative.

Findings with regard to the primary renal tumors in male rats are summarized in Table 1. Exposure was for 6 hr/day, 5 days/week for 107 weeks. All of these primary renal tumors were observed in rats which died after 18 months or when the experiment was terminated at 24 to 26 months. In serial sacrifices during the first year there was observed early and progressive renal tubular disease. In the second year preneoplastic changes were observed, and it is believed that these preceded the development of the primary renal tumors.

Findings in the male rat are particularly important since spontaneous renal tumors are rare in these animals. A preliminary draft of these findings was reviewed by the Cancer Assessment Group at the Environmental Protection Agency and they concluded that the study furnished sufficient evidence for carcinogenicity of unleaded gasoline vapor in rats and mice under the conditions of the bioassay and that the evidence for the carcinogencity of unleaded gasoline vapor in rats and mice indicates that this material could be considered a potential human carcinogen (*2*). They considered the carcinogenic potency of gasoline to be relatively low, however, lower than benzene or vinyl chloride.

This is a review of the literature to see whether there is any support for the animal findings in human experience. The animal model suggests that, if gasoline exposure causes kidney cancer in man, it is likely that there would be a very long exposure period and a long latent period so that any effects of gasoline exposure in an exposed population would probably be in older age groups. Also, based on the EPA potency estimates of gasoline as a carcinogen and based on the probability of a low exposure level (in relationship to the animal exposure) for human populations, if there are any effects in humans they are likely to be small and difficult to detect epidemiologically.

In the following, the epidemiologic evidence will be examined under three headings: ecologic studies, which provide the weakest kind of evidence; cohort studies which provide strong evidence but which sometimes fail to control for confounding variables; and case control studies which lack the power of cohort studies but which

Table 1. Gasoline exposure and primary renal neoplasms in male rats.

Level of exposure, ppm	No. of rats exposed	Neoplasm	Number of neoplasms
0	100	None	0
67	100	Carcinoma	1
292	100	Adenoma	2
		Carcinoma	2
		Sarcoma	1
2056	100	Carcinoma	6
		Adenoma[a]	1

[a] Occurred in male rat at 18 months.

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often provide an opportunity to control for confounding variables.

Ecologic Studies

Ecologic studies are investigations that use groups as the unit for analysis and which associate attributes of groups. Grouping can be people living in the same time period (temporal), people living in the same geographicalarea(spatial)orbycharacteristicssuchasrace,religion, or ethnic origin. The advantages and limitations of this kind of analysis have been reviewed by Morgenstern (*3*).

Figure 1 shows per capita gasoline production in the United States for the period 1916–1977 (*4–6*). The greatest growth occurred between 1916 and 1941 following closely the growth in automobile ownership. During that period, per capita production rose 10-fold, from approximately 0.5 bbl per capita in 1916 to 5 bbl by 1941. In the next 40 years, annual production doubled to approximately 11 bbl per capita. In the US production and consumption are almost identical so that U.S. per capita production can be treated as consumption data.

Kidney cancer mortality rates have also been rising in the United States. Age-adjusted mortality rates increased 40% among white males and 76% among black males between 1950 and 1977, while age-adjusted mortality rates among white females and black females rose 10% and 24%, respectively, over the same period. Recent annual mortality rates were 4.5 per 100,000 for white males, 3.1 per 100,000 for black males, 2.1 per 100,000 for white females, and 1.6 per 100,000 for black females (*7*). According to the Third National Cancer Survey, incidence rates were 8.9 per 100,000 for white males, 7.6 for black males, 4.0 for white females, and 3.8 for black females (*8*).

Figure 2 shows that during the period 1950–1977 the increase in kidney cancer mortality among white males was largely attributable to an almost twofold increase in the mortality rate among males 75–84 years of age. There was also an increase in males 65–74 years of age;

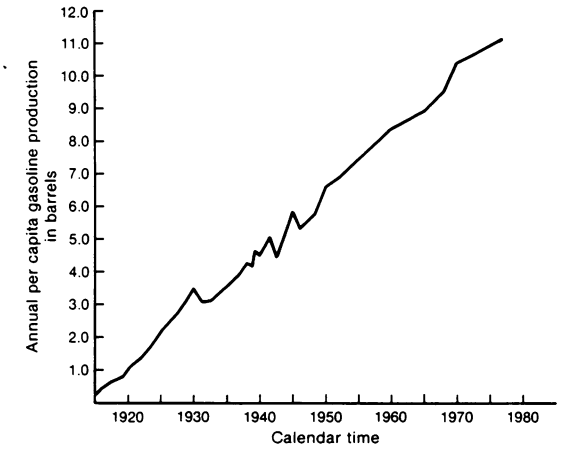

FIGURE 1. Per capita production of gasoline in the U.S., 1915–1977.

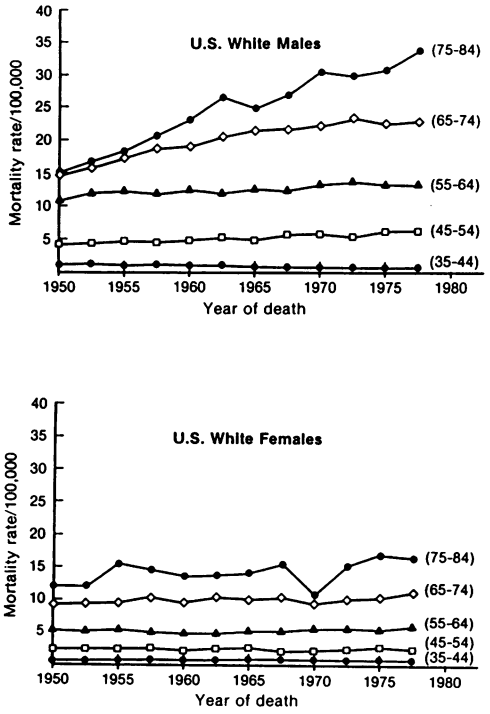

FIGURE 2. Renal cancer mortality for selected ages, 1950–1977.

however, the degree of change was relatively small. On the other hand, age-specific mortality among white females was relatively stable in most age groups although there was some increase in the age group 75–84.

An interesting feature of kidney cancer mortality is the increasing difference between males and females. The increase in male mortality rates started at least as early as 1930 (*9*). Davis et al. note that the male/female ratio of mortality rates went from 1.20 in 1935 to 2.16 in 1970 (*10*).

The potential for gasoline exposure and death rates for kidney cancer are both rising. Moreover gasoline exposure is probably greater for males than for females. Thus gasoline exposure could be a reason for the pattern of increases in kidney cancer mortality. This is, however, a very crude comparison confounded by many variables and this kind of ecological correlation provides perhaps the weakest kind of epidemiologic evidence of cause and effect.

There are large international variations in both kidney cancer mortality and in gasoline consumption (*11*). Figures 3 and 4 show the association between per capita annual gasoline consumption and kidney cancer for males and for females for 40 countries (*4,11*). The high consumption in Australia, Canada, and the U.S. is notable as is the relatively narrow range for the rest of the world. Clearly there is some association here between gasoline consumption and kidney cancer. Like trends shown in Figures 1 and 2, however, this evidence is not compelling. Gasoline consumption is a surrogate measure of economic and industrial development throughout

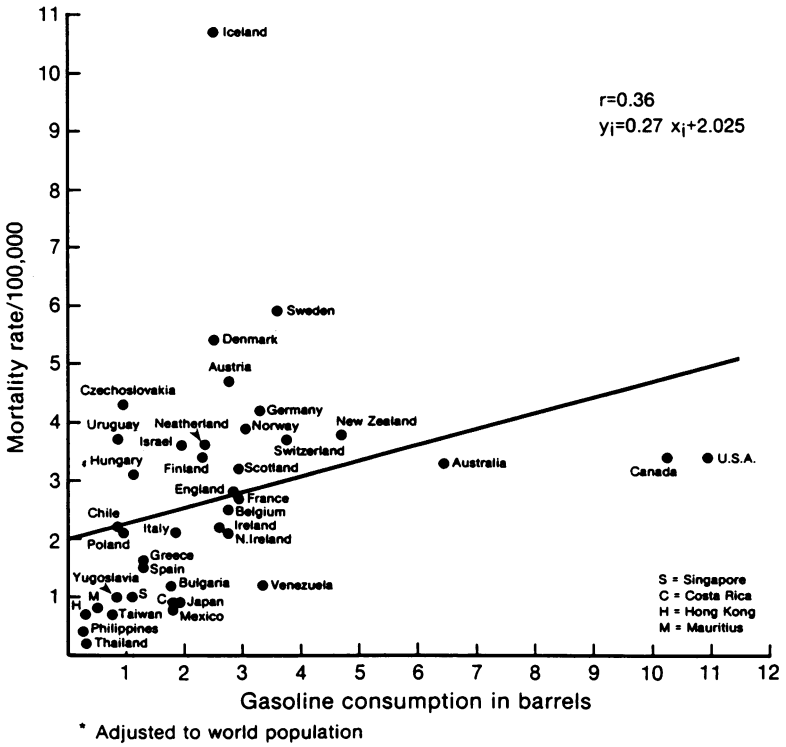

FIGURE 3. Annual per capita gasoline consumption in 1980 and age-adjusted renal cancer mortality among males for 40 countries, 1970.

the world. Thus, although an ecologic correlation of low order exists, it is unlikely that this is important evidence for a causal relationship between gasoline exposure and kidney cancer.

Ecologic units, other than temporal and spatial units, have been related to kidney cancer. These include race, religion, ethnic origin, social class, occupational groupings, and urbanization. Incidence and mortality is slightly higher for whites than nonwhites and this tends to be so for every age group (*12*). Jews appear to be at increased risk, and this is true for both males and females, while Mormons have generally lower kidney cancer mortality than other U.S. whites (*13–15*). Migrant studies of the Chinese show that kidney cancer mortality of Chinese in Taiwan is low in both males and females compared with Chinese in the U.S. (*16*). Migrant Mexican-Americans in the U.S. (Los Angeles County) have lower incidence rates than indigenous Mexican-Americans (*17*). McLaughlin et al. (*18*) in a case-control study of renal cell carcinoma, found a relationship with German, Scandanavian, and Irish ethnicity and concluded that ethnic factors account in part for a clustering of renal cancer in the North Central area of the United States. Incidence and mortality rates appear to be higher among Alaskan natives than in the U.S. (*19*). These patterns by race, religion and ethnic origin do not provide any consistent evidence of a role for gasoline exposure in the etiology of kidney cancer.

In England and Wales, social class is positively associated with kidney cancer mortality at ages 65 and over, with the highest rates in the highest social class (*20*). This observation is based on a grouping of occupations to form social classes, and combining occupational data appearing on death certificates with occupation as enumerated in a census. A similar study in the United States showed no overall trend with social class, although there was a slight excess in the highest social class (*21*). In a study of correlates of geographic patterns in the U.S., Blot and Fraumeni found increased mortality associated with higher socioeconomic status (*22*). Two case control studies, however, did not detect an association between renal cell carcinoma and either education, income or social class (*23,24*). National occupational mortality statistics for England and Wales have been reviewed by McLaughlin and Schuman for the years 1959–1963 and 1970–1972 to see in which occupations kidney cancer is in excess (*12*). For 1970–1972, occupational data for England and Wales show only two occupational groupings with statistically significant excesses in kidney cancer: commercial travelers and manufacturing agents, and administrators and managers. In general, social class and occupational differences in kidney cancer do not suggest gasoline as etiologic agent in kideny cancer.

Most studies show a higher kidney cancer incidence and mortality rate in urban as compared with rural areas. Blot and Fraumeni (*22*) noted a modest association between urbanization and elevated renal cancer mortality for males. A positive trend in age-adjusted mortality with increasing urbanization was most apparent in the

Southern U.S. Other studies also have noted this urban/rural difference (*25–28*). Data from the Connecticut Tumor Registry for the period 1935–1971 show a large urban/rural gradient in kidney cancer incidence with an urban/rural ratio of incidence rates of 2.12 for males and 1.58 for females in that state (*29*). Gasoline exposure could be related to these urban-rural differences.

Three studies have looked at petroleum refining in an ecologic context. Wen has examined the kidney cancer mortality for two counties in Texas where there is a very heavy concentration of refineries and petrochemical plants and where it can be assumed that male residents have experienced higher than average exposures to hydrocarbons (*30*). He compared this to kidney cancer mortality in the entire U.S. There were 99 male deaths for the years 1965–1981 for these two counties at ages 15 and older. Based on the mortality experience of the U.S. male population adjusted for age, race and calendar time the expected number of deaths was also 99. Thus there was no excess mortality from kidney cancer in these counties compared with the entire U.S.

Blot et al. (*31*) related kidney cancer death rates in U.S. counties for the period 1950–1969 with the presence of petroleum industries in these counties. Thirty-nine counties were selected where at least 100 persons were employed in petroleum manufacturing and where these employees constituted 1% or more of the county population. Nearly all these 39 counties had petroleum refineries since 1940 and over half were located in Texas, Louisiana, Arkansas, Oklahoma, and Kansas. The age-adjusted mortality for kidney cancer in these 30 counties was compared with a control group of 117 counties comparable by geographic region, population size, percentage urban, population density, median school years completed by the adult population, median family income, percentage nonwhite, and percentage foreign born. For kidney cancer the ratio of the age-adjusted death rates for white males for the period 1950–1969 in the petroleum industry counties to the control counties was 1.05. This did not differ significantly from a ratio of 1.00 ($p > 0.05$).

Hearey et al. have compared the incidence of kidney cancer during the years 1971–1977 in sections of the San Francisco Bay Area where there were petroleum and chemical industries with areas where there were none (*32*). The mean annual incidence per 100,000 in areas with petroleum and chemical industries was 10.4 among males and 2.6 among females, whereas the mean annual incidence in areas without these industries was 7.0 among males and 3.0 among females. These differences were not commented on by the authors.

These three ecologic studies related to petroleum refining do not support a role for gasoline as a cause of kidney cancer.

Cohort Studies

In cohort studies individuals form the study unit, whereas in ecological studies units are years, counties, country, or ethnic group. Individuals exposed to hydrocarbons are populations of workers in petroleum refineries and in gasoline marketing terminals. The most common measure of exposure here is total hydrocarbons and that was the measure of gasoline exposure used in the animal studies. Wen has reported on hydrocarbon exposures at refineries and at marketing terminals (*30*). These data are shown in Table 2. Exposure levels, while generally below the levels developed for the animal experiments, are not entirely out of range of the animal exposures. For refineries, 5% of all personal 7-hr samples taken were above 20.4 ppm, while for marketing terminals, 5% were above 30.0 ppm. Exposure levels were a little higher at marketing terminals than at refineries.

There are currently available in published or unpublished form 12 cohort studies, 11 of oil refinery populations and one of a population of petroleum products distribution workers. There is an unknown amount of overlap among some of these populations and for some populations there has been more than one report. Most of the studies were not directed at the question of an excess in kidney cancer deaths and from this standpoint some of the reports are not very informative. Only one of the studies includes data on cigarette smoking and cigarette smoking is one of the few agents believed to be related to kidney cancer (*12*). Thus, high or low kidney cancer incidence or death rates could be related to high or low smoking rates. Some clue as to the smoking habits of the 12 populations covered by the cohort stud-

Table 2. Hydrocarbons measured at petroleum refineries and marketing terminals.

Site	Type of sample	Number of samples	Mean, ppm	Standard deviation, ppm	Hydrocarbons, ppm		
					At 5%	At 50%	At 95%
Refineries	Personal sampler						
	≥ 7 hr	1201	5.4	16.5	0.15	1.8	20.4
	< 7 hr	216	13.7	49.5	0.10	3.7	60.0
	Area sampler	1400	15.2	103.3	0.02	2.2	50.0
Marketing terminals	Personal sampler						
	≥ 7 hr	66	11.2	19.0	0.05	5.4	30.0
	< 7 hr	1491	71.5	182.4	0.26	13.0	340.0
	Area sampler	390	13.4	37.8	0.08	3.1	46.7

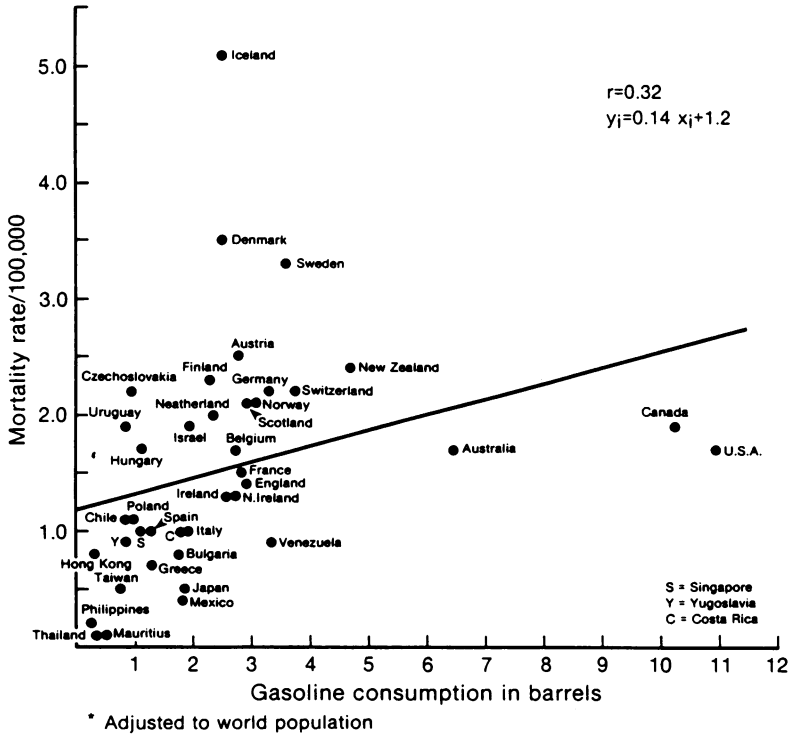

FIGURE 4. Annual per capita gasoline consumption in 1980 and age-adjusted renal cancer mortality among females for 40 countries, 1970.

ies can be obtained, however, by examining the mortality experience of these populations from lung cancer and from nonmalignant respiratory disease, since these diseases are very highly related to cigarette smoking.

Of the 12 studies, one does not define the population at risk and deals only with deaths. For that study findings are based entirely on the calculation of proportionate mortality ratios (PMRs). Here the comparison group was the population of the entire United States. The deaths studied occurred during the years 1943–1979 and were those known to the Oil, Chemical and Atomic Workers International Union (*33*). Three oil refineries and "small petrochemical operations" from the Beaumont-Port Arthur area of Texas were represented. The PMR for kidney cancer adjusted for time, age, and race was 137 based on 15 deaths. Had the observed number of deaths been the same as the expected, the PMR would have equaled 100. A PMR of 137 means that there was a 37% excess in kidney cancer deaths. Lung cancer was slightly elevated (PMR = 114), while nonmalignant respiratory disease was in deficit (PMR = 57). Taken together, these last two causes of death suggest that smoking patterns in this population were not unusual. The authors did not attach importance to the kidney cancer deaths. This study was a refinement of an earlier study in that the more recent study included retirees. The earlier study provided some additional details on kidney cancer, however, in that data were shown by length of union membership (*34*). For white males who were union members less than 20 yr, the PMR was 93 based on 5 deaths, while for those who were members 20 years or more the PMR was 214 based on 7 deaths, and this excess was statistically significant ($p < 0.05$).

One of the earliest epidemiological studies of oil refinery workers was by Tabershaw-Cooper Associates (*35*). This covered 20,163 workers from 17 oil refineries in the U.S. Workers were included who worked for a least 1 yr between 1962 and 1971. All workers were traced for deaths through 1971. Of the 20,163 workers, 76% had been hired before 1952. Kidney cancer was not shown separately in the original report, but there was a large deficit in a broader cause of death category—urinary cancer—with a standardized mortality ratio (SMR) of only 36 based on 6 observed deaths. SMRs can be interpreted like PMRs. Respiratory cancer was also in deficit, with an SMR of 80, suggesting that this population of 20,163 workers may have smoked less than the U.S. population. For workers hired before 1952, the SMR for urinary cancer was 37 based on 6 deaths and for respiratory cancer 82 based on 90 deaths. Jobs were classified as high, medium, and low with regard to hydrocarbon exposure. SMRs for urinary cancer were as follows: high 27 (2 deaths), medium 40 (3 deaths), and low 48 (1 death). Thus, there was no evidence of a positive dose-response relationship for urinary cancer. For respiratory cancer, SMRs were 88, 74, and 66 for high, medium, and low exposures, respectively. A 1975 report in which follow-up was improved by using social security records showed almost identical results with regard to urinary and respiratory cancer.

In 1982 this study was updated by Kaplan through 1976 (*36*). In the update, the SMR for urinary cancer was 54, while for kidney cancer it was 69 based on 11 deaths. The SMR for respiratory cancer was 77. Details on kidney cancer were also provided through 1971, the end of follow-up in the earlier report. Here it was shown that the SMR for kidney cancer in the earlier report was actually 46 based on 4 deaths. Kaplan commented specifically that there did not appear to be any excess of renal cell carcinoma in this large cohort of workers.

In 1984, Hanis et al. reported on a study of 15,437 employees who worked one month or more during the period 1970–1977 plus 6,261 retirees alive January 1, 1970, from three Exxon refineries and chemical plants (*37*). The kidney cancer SMR was 143 for the entire cohort based on 22 deaths and 95 for lung cancer based on 209 deaths. Kidney cancer SMRs were elevated at each of the three locations studied: 155, 123, and 149. None of these excesses were statistically significant. For workers 15 years or more after first hire, the SMR for kidney cancer was 147 based on 22 deaths. Hanis et al. also reported on internal comparisons for this same cohort and on smoking histories (*38*). Of the 22 kidney cancer deaths, 16 occurred among workers for whom smoking histories were available. Of these 16, only one had never smoked. Numbers are too small to compare kidney cancer deaths in smokers with nonsmokers. In an earlier study, Hanis et al. had reported on only one of the three plants (*39*). In that study they reported a kidney cancer SMR of 155 based on 9 deaths. For a subpopulation of operators, mechanics, and laborers, a group more likely to be exposed to hydrocarbons, the SMR for kidney cancer was 205 based on 9 deaths.

In 1983 Wen et al. reported on the mortality experience of 16,880 workers from the Gulf Oil Refinery at Port Arthur, TX (*40*). Some petrochemicals were produced including benzene, cumene, ethylene and cyclohexane. Workers employed sometime between 1937 and 1978 were followed through 1977. The SMR for kidney cancer was 112 based on 22 deaths. For workers employed a year or more the SMR was 127 based on 16 deaths for whites and 132 based on 3 deaths for nonwhites. For these same workers the lung cancer SMR was 105 for whites and 78 for nonwhites. The slight elevation in the SMR for kidney cancer was not commented on. A more recent report on the same refinery shows that for hourly male workers at ages under 60 the SMR for kidney cancer was 109 based on 9 deaths, while at ages 60 and over the SMR was 135 based on 13 deaths (*30*). For workers exposed less than 20 yr the SMR was 103 based on 8 deaths, while for workers exposed 20 yr or more the SMR was 138 based on 14 deaths.

Also in 1983, Divine et al. reported on the mortality experience of 19,077 white male refinery, petrochemical, and research workers from the Texaco Company who worked at least one day during the period 1947–1977 and who were employed 5 yr or more (*41*). A total of 24 kidney cancer deaths were observed, and the SMR was 93. A petroleum refinery at Port Arthur, TX, was reported on separately. Twelve kidney cancer deaths were observed here, and the SMR was 97. Lung cancer and nonmalignant respiratory disease SMRs were low.

In 1979 Hanis et al. reported on a study of 15,032 male terminated workers with 4 yr or more service at refineries and chemical plants owned by the Imperial Oil Company of Canada plus workers active at the end of the study with more than 1 yr service (*42*). In this study they compared age adjusted death rates for exposed and nonexposed workers for the years 1964–1973. Exposure was defined as daily occupational contact with petroleum or its products. Kidney cancer was not separately identified. For cancer of the urinary bladder and kidney, the age-adjusted death rate per 100,000 was 2.6 (14 deaths) in exposed workers and 2.4 (5 deaths) in nonexposed workers. The risk ratio for urinary cancer was 1.08. This was not discussed as to its probable importance. For respiratory cancer the risk ratio was 1.18. When the population was subdivided into refinery and nonrefinery workers the risk ratio for urinary cancer was 1.19. Refinery workers were defined as those performing daily work on the refinery site.

In 1979, Theriault and Goulet studied 1205 men who worked 5 yr or more at a Canadian oil refinery near Montreal, Canada (*43*). For a broad category of deaths due to genito-urinary cancer they reported an SMR of 117 based on 3 deaths. None of these deaths were due to kidney cancer.

In 1981, Rushton and Alderson reported on the mortality of 34,781 workers from 8 oil refineries in Great Britain (*44*). This cohort had been employed at least 1 yr between January 1, 1950, and December 31, 1975. The SMR for kidney cancer was 101 based on 22 observed deaths. Both lung cancer and bronchitis deaths were in deficit.

Raabe, in a 1983 review of kidney cancer epidemiology in petroleum-related studies, reported on a preliminary draft of a study of 4733 white males employed at least 1 yr during the years 1945–1979 at a Mobil Oil Company refinery at Beaumont, TX (*45*). The SMR for kidney cancer at that refinery was 74 based on 5 deaths. For lung cancer the SMR was 92.

In 1983 Morgan and Wong reported on a study of 14,179 workers at two refineries owned by Chevron USA (*46*). The cohort consisted of all persons working at either refinery for 1 yr before December 31, 1980, and who worked there at least 1 day between January 1, 1950 and December 31, 1980. The kidney cancer SMR was 88 based on 13 deaths. For workers with less than 20 years employment the SMR was 156 based on 7 deaths, and for employment 20 years or more the SMR was 58 based on 6 deaths. They concluded that there was no suspicion of an excess risk for kidney cancer.

Perhaps the study most relevant to the question as to whether gasoline exposure is related to kidney cancer in humans is a second but unpublished study by Rushton and Alderson (*47*). In that study, 23,358 men who worked at distribution centers for three oil companies in Great

Table 3. Standardized mortality ratios for kidney cancer by duration of exposure.

Study	Duration of exposure (deaths)[c]	
	< 20 yr	≥ 20 yr
Thomas et al. (*34*)[a]	93 (5)	214 (7)
Wen (*30*)	103 (8)	138 (14)
Rushton and Alderson (*47*)	78 (6)	150 (17)
Morgan and Wong (*46*)[b]	156 (7)	58 (6)

[a] Length of union membership.
[b] Duration of exposure less than 15 years and 15 years or more.
[c] Number of kidney cancer deaths observed in parentheses.

Britain were studied. Distribution workers are interesting since they probably have greater hydrocarbon exposures than refinery workers. The SMR for kidney cancer was 120 based on 21 deaths. There was an excess among drivers with an SMR of 171 based on 12 kidney cancer deaths and the excess appeared to be related to long service. For workers, excluding drivers, the SMR was 90 based on 10 deaths. Thus all of the excess was among drivers. For workers with less than 20 yr service, including drivers and nondrivers, the SMR was 78 based on 6 deaths and for workers with 20 yr or more service the SMR was 150 based on 7 deaths. Cancer of the lung was in deficit as was bronchitis.

In 1981, Schottenfeld et al. (*48*) made a preliminary report on a prospective morbidity study of workers from 19 U.S. petroleum and petrochemical companies. They reported a standardized incidence ratio (SIR) for kidney cancer of 94 for refinery workers based on 8 cases.

Cohort studies of gasoline refinery and distribution workers do not appear to support the notion of a relationship between gasoline exposure and kidney cancer. However, most of these studies were not designed or analyzed with a gasoline exposure–kidney cancer hypothesis in mind and few data are available on duration of exposure or time since first exposure in relation to kidney cancer.

Table 3 shows the data available on kidney cancer SMRs or PMRs by length of exposure for four of the 12 populations studied by the cohort method. For three of these there does appear to be an excess in kidney cancer after 15–20 yr or more of exposure while for the fourth the largest excess is in the shorter exposure group. None of the excesses are statistically significant.

There is some evidence for seven of the 12 populations studied that the age of these populations differed considerably. An inference about this can be made by examining the ratio of the expected number of deaths from bladder cancer to the expected number for kidney cancer. The ratio of these two numbers is an index related to the age of the populations studied. In the U.S. population the mortality rate for bladder cancer among white males is roughly twice the mortality rate for kidney cancer, so that for a population distributed by age like the U.S. population this ratio would be about 2. The age-specific mortality rates for bladder and kidney cancer for U.S. white males and females are shown in Figure 5. The reason for the bladder cancer excess in the U.S. white population is clearly a very high bladder cancer death rate at older ages. For younger persons, death rates for bladder cancer and kidney cancer are not much different. All the U.S. cohort studies calculated expected deaths by applying age-time-specific U.S. death rates like those shown in Figure 5 to age-time-specific person-years lived by the cohort being studied. This same method was used for the British cohort studies but using as the standard death rates for England and Wales. Thus, the expected number of deaths for each cause represents national rates weighted by the age distribution of the person years lived by the population studied.

Five of the U.S. cohort studies and both of the British studies show the expected number of deaths for bladder and for kidney cancer, so that for these studies the ratio of expected bladder to expected kidney cancer deaths can be calculate. If this ratio is low then the population

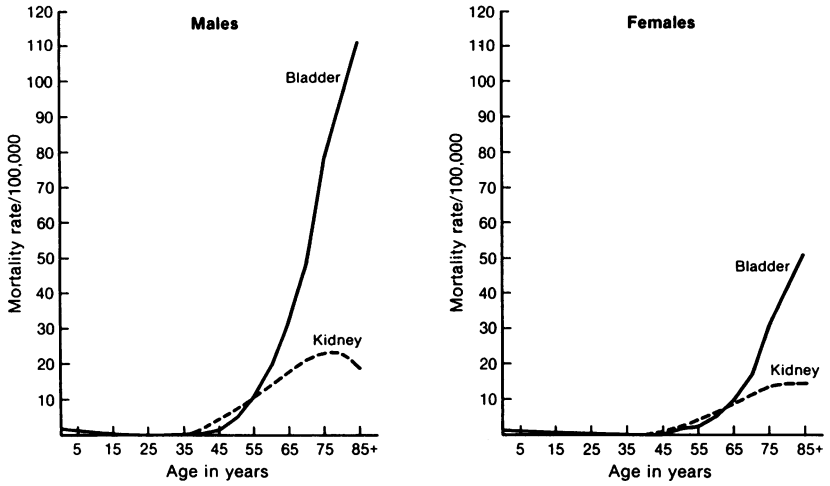

FIGURE 5. Age-specific bladder and renal cancer mortality among U.S. white population, 1950–1969.

Table 4. Standardized mortality ratios (SMR) for kidney and lung cancer by an index of population age.

Study	Index of age[a]	SMR	
		Kidney cancer	Lung cancer
American studies			
Kaplan (*36*)	1.06	69	80
Morgan and Wong (*46*)	1.30	88	67
Divine et al. (*41*)	1.37	93	58
Wen et al. (*30*)	1.42	112	99
Hanis et al. (*37*)	1.64	143	95
British studies			
Rushton and Alderson (*44*)	2.03	101	78
Rushton and Alderson (*47*)	2.25	121	80

[a] Ratio of expected bladder cancer deaths to expected kidney cancer deaths.

studied must lie to the left on Figure 5. If this ratio is high, then the population must lie to the right.

These ratios are shown in Table 4 along with SMRs for kidney cancer and for lung cancer. There does appear to be an association here between this age index and kidney cancer. When the population studied was young, the SMR for kidney cancer was low. When the population studied was old the SMR for kidney cancer was higher. Moreover the ratio is not strongly associated with the SMRs for lung cancer suggesting that this age effect may be specific for kidney cancer.

A conclusion that could be drawn from Table 4 is that there is a kidney cancer excess that shows up in refinery workers at old ages. There may be two reasons for low SMRs in most U.S. studies of refinery populations. First, refinery populations may smoke less than the general population of the U.S. and thus tend to have a lower kidney cancer death rate. Second, these studies are heavily weighted by person-years lived at young ages, so that if hydrocarbon exposure causes kidney cancer at older ages these effects would be diluted. The latter reason suggests that if follow-up were to continue or if an older population were studied, SMRs for kidney cancer might have been somewhat higher than those observed.

Case-Control Studies

Like cohort studies, these are studies of individuals and while they sometimes lack the power of cohort studies they often have an advantage in allowing for extensive control of confounding variables. There have been three case-control studies focused primarily on the role of gasoline related exposure in kidney cancer. In 1981, Gottlieb and Carr reported on a death certificate study of kidney cancer deaths during the years 1960–1975 in parishes of Louisiana in which 1% or more of the population were employed in the petroleum, chemical and paper industries (*49*). The proportion of deaths due to kidney cancer for which the death certificates listed an occupation associated with employment in petroleum refineries and petrochemical industries was compared with the proportion of noncancer deaths which listed these occupations. These two groups were matched by parish of usual residence at death, age at death, year of death, race and sex. The estimated relative risk for kidney cancer was 2.27, and this is statistically significant ($p < 0.05$). Since there was matching by residence this excess in kidney cancer was unlikely to be due to the source of drinking water which was shown in a subsequent study to also be associated with kidney cancer in Louisiana (*50*). On the other hand, according to Gottlieb and Carr, the petroleum industry only became a major employer in Louisiana in the 1960s. If this type of employment is related to kidney cancer, and if there is a long latent period, its unlikely that deaths for the years 1960–1975 would be much affected.

Wen (*30*) reported on a case control study of 22 kidney cancer deaths which occurred during the years 1937–1978 among refinery workers at one Gulf Oil Company refinery. Gasoline exposure of these cases was compared with that of two sets of controls for each case, 3 deceased controls and 3 mixed controls (deceased and alive). Cases and dead controls were matched on race, sex, date of birth, date of death and length of employment while cases and mixed controls were matched on race, sex, date of hire and date of birth. For workers exposed to gasoline 5 yr or more, the estimated relative risk calculated by using deceased controls was 0.87 and by using mixed controls 1.38.

Divine et al. (*41*) reported on a case-control study of 24 white male kidney cancer deaths observed in their cohort study. Controls were randomly selected from the cohort of noncase white males who had a work history record and who died after the age of 30. They found no difference between cases and controls for job categories where there may have been exposure to gasoline and middle distillates.

These three case-control studies lend little support to the notion that gasoline exposure causes kidney cancer in humans.

Studies of Other Hydrocarbon Exposure

There have been many studies of the effects of exposure to high boiling hydrocarbons, however, these have focused on cancers of the skin and lung, and most do not show kidney cancer separately. In a recent case-control study of renal cell carcinoma, however, McLaughlin et al. found a significant ($p < 0.05$) association with work in occupations involving exposure to petroleum tar and pitch (*18*). Workers exposed to bituminous residues of petroleum have been studied elsewhere but results are difficult to interpret due to the probability that coal tar exposures also occurred. Coal tar is believed to have a much higher potential for carcinogenesis than petroleum tar. Perhaps the most striking obser-

vation made with regard to a kidney cancer excess was among workers exposed to coal tar in coal coking operations where a relative risk of 7.5 was observed based on 8 kidney cancer deaths (*51*). A few studies of chemical workers, where exposure to halogenated hydrocarbons occur, also suggest a relationship of these hydrocarbons to kidney cancer (*52–55*). It is unclear as to how these observations relate to the question of whether gasoline causes kidney cancer in humans.

Conclusion

This review of the epidemiologic literature does not provide consistent evidence for a relationship between gasoline exposure and kidney cancer in man. Ecologic data, which relate trends in the production of gasoline to trends in kidney cancer deaths or which relate national gasoline consumption to kidney cancer deaths, are supportive of a relationship but provide the very weakest kind of epidemiologic evidence. The large number of cohort studies of petroleum refinery or distribution workers are not generally supportive of a relationship, but most of these studies were not designed or analyzed to examine this relationship. Taken together these studies provide some evidence of a small kidney cancer excess among older workers, or among workers exposed for long periods. Two case-control studies dealing with internal comparisons of refinery populations have been negative. Because of the potential for human exposure to gasoline further study of exposed populations is needed.

ADDENDUM: After hearing the presentation of this paper at the Fifth Annual Symposium on Environmental Epidemiology, Dr. Samuel Milham, Department of Social and Health Services, State of Washington wrote (May 2, 1984) pointing out that the proportionate mortality rates (PMRs) for the State of Washington show a PMR for fuel oil truck drivers (including gasoline truck drivers) for the years 1950–1981 of 254 based on five kidney cancer deaths. Four of these deaths occurred during the years 1970–1981 when the PMR was 319. All deaths were at ages 65 or older.

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