

# Renal Cell Cancer and Exposure to Gasoline: A Review

by Joseph K. McLaughlin

A review of the epidemiology of renal cell cancer is presented. Risk factors for renal cell cancer such as cigarette smoking, obesity, diet, and use of analgesics and prescription diuretics are examined. Although uncommon, occupational risk factors are also reviewed. Studies examining gasoline exposure and renal cell cancer are evaluated, including investigations recently presented at a meeting on this topic. Overall, most studies find no link between gasoline exposure and renal cell cancer; moreover, the experimental evidence that initiated the health concern is no longer considered relevant to humans. Positive associations, however, reported in two recent studies prevent a firm conclusion of no risk for this exposure.

## Background

Kidney cancer accounts for about 2% of all new cancer in the United States (1). In 1991 there were approximately 25,300 new cases of kidney cancer and about 10,600 deaths, with 60% of the new cases and deaths occurring among men and 40% among women (2). The major tumors found in the adult kidney are renal cell cancer and renal pelvis and ureter cancers, accounting for 70, 15, and 8%, respectively (3). Contrary to earlier reports, renal cell cancer does not account for 80-90% of all renal tumors among adults (3). Renal cell cancer develops in the parenchyma of the kidney, whereas renal pelvis tumors develop in the collecting area of the kidney leading to the ureter, which in turn leads to the bladder.

The incidence rate for renal cell cancer is 8.4 per 100,000 among white men, 8.6 among black men, 3.7 among white women, and 3.8 among black women (3). Rates for renal pelvis and ureter cancer are much lower, averaging between one and two per 100,000 for men and women of both races. Incidence rates have been increasing in renal cell cancer an average of 2% per year and increasing 3% per year for renal pelvis and ureter cancers (3).

Internationally, incidence rates for renal cell cancer are highest in Scandinavia, North America, and Western Europe, and rates are lowest in Asia, Africa, and South America (1). Survival with these tumors is moderate to good, depending on the site and stage of the cancer. For renal cell cancer, the 5-year relative survival rate is about 50%, but for patients with renal pelvis or ureter cancers the rate is approximately 65% (1). In this review informa-

tion on renal cell cancer will be presented whenever possible; however, many studies report data only for all kidney cancers combined. Results from these studies will be referred to as kidney cancer.

## Risk Factors

Cigarette smoking is causally linked to renal cell cancer, as demonstrated in a number of case-control and cohort studies (1,4). Risk ratios range from about 1.5 to 2.5 for this exposure. About 30% of the cases among men and 25% among women can be attributed to cigarette smoking (5). Another risk factor reported in virtually all studies of this cancer is high relative weight or obesity. When measured by the body mass index (weight/height<sup>2</sup>), which accounts for height, the risk of renal cell cancer increases with the level of the body mass index. The association has been observed more strongly in women than men. Recently, this association has been reported in China, a country with low rates of obesity (6). Heavy use of phenacetin-containing analgesics has also been linked to an increased risk of renal cell cancer (6-9). In case-control and cohort studies, use of prescription diuretics have been linked to renal cell cancer (10-13).

Dietary factors such as high intake of meat (5,6,14) and fat (15) have increased the risk of renal cell cancer, whereas intake of fruits and vegetables have decreased the risk (6,14,15). Consumption of coffee, tea, or alcoholic beverages has generally not been found to increase risk (1).

Renal cell cancer is not usually thought of as an occupationally associated tumor as is bladder cancer. However, a number of studies have reported an association with exposure to asbestos (16-19). Coke oven workers have also been reported to be at increased risk (20). Cadmium has been linked to an increased risk of renal cell cancer in one early study (21), but has not been associated in later, larger

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case-control studies or in occupational cohort investigations (1). Inorganic lead has induced renal tumors in laboratory animals, although there is no epidemiologic support for an association in humans (22). Proportional mortality studies (23–26) and one case-control study have reported excess kidney cancer mortality among dry cleaning and laundry workers (27). However, a recent large-scale cohort study of these workers showed no increase in kidney cancer mortality (28).

A number of other occupational associations with kidney cancer have been reported. Elevated mortality from kidney cancer was observed among newspaper pressmen (29), although this finding has not been confirmed (30). An increased risk for truck drivers (31) and for workers exposed to polychlorinated biphenyls (32) has also been observed.

A large number of cohort studies of petroleum refinery workers have examined cancer risk (33). In a meta-analysis of data from these studies, no excess risk was observed for kidney cancer [standardized mortality ratio (SMR) = 0.98, based on 147 cases] (34). Other reviews of cancer risk among petroleum refinery workers found little evidence to support an association with kidney cancer (33). The focus of the remainder of this review will be the specific issue of gasoline exposure and renal cell cancer.

## Gasoline and Renal Cell Cancer

Another occupational exposure, gasoline, became suspect after male rats developed a significant excess of renal tumors as a result of long-term exposure to unleaded gasoline vapors (35). After this report a number of epidemiologic studies examined gasoline exposure. One case-control study of renal cell cancer in Minnesota showed a slight upward trend in risk with years of employment as a service station attendant (36). The trend test was not statistically significant nor were the individual point estimates. A case-control study in New York state found no association between gasoline and renal cell cancer (37). No case-control differences in gasoline exposure were observed in a study in Los Angeles (10). Two nested case-control studies evaluating gasoline exposure among petroleum refinery workers found no association with kidney cancer mortality (38,39). Although a case-control screening study of exposure to petroleum-derived liquids found a significant association between kidney cancer and aviation and jet fuels (40), a recent follow-up of aircraft maintenance workers showed no association with kidney cancer risk (41). Recently, a case-control study in Finland reported a significant association between renal cell cancer and gasoline with a dose-response effect for level of exposure but not for duration (42). Findings from a new large-scale population-based, case-control study of renal cell cancer in Australia showed no association with employment in gasoline service stations or exposure to gasoline (19). Results from a large-scale case-control study in the Boston area also revealed no link with gasoline exposure (M. Maclure, personal communication).

## New Findings

Poole and colleagues (43) reported findings from a nested case-control study of kidney cancer mortality among male petroleum refinery workers from five U.S. companies. Occupational histories were abstracted from employment records for 102 cases and 408 controls. Extensive semiquantitative exposure ratings were assigned by industrial hygienists blind to the case or control status of the subjects, with particular attention to potential gasoline exposure. No excess risk [relative risk (RR) = 1.00, 95% CI: 0.51–1.94] of kidney cancer was observed for exposure to gasoline, regardless of measure used: cumulative exposure, years prior to diagnosis, age at diagnosis, age at hire, or year of hire. In an analysis of longest job held, three occupations with increased RRs were identified: laborers (RR = 1.94, 95% CI: 0.96–3.92; 24 cases, 53 controls); workers in receipt, storage, and movement (RR = 2.49; 95% CI: 0.95–6.56; 9 cases, 15 controls); and unit cleaners (RR = 2.28, 95% CI: 0.53–9.93; 3 cases, 5 controls). Exposures for these three groups of workers in a refinery are varied. The one group with enough subjects to allow further analysis, laborers, has the most difficult job to assess due to the nonspecific nature of the job.

Wong et al. (44) presented results from a cohort mortality analysis of 18,135 U.S. gasoline distribution employees, split about evenly between land-based terminal and marine vessel workers. Quantitative exposure measures to assess gasoline exposure were used to define the cohort. Potential exposure to gasoline for at least 1 year was needed to enter the cohort. No relation between gasoline exposure and kidney cancer mortality was observed. The SMR for the land-based workers was 65.4 (95% CI: 33.7–114.1; 12 deaths) and for marine vessel workers was 83.7 (95% CI: 45.8–140.5; 12 deaths). Measures of exposure such as duration, age at first exposure, year of first exposure, cumulative exposure, or frequency of peak exposure had no relation to risk of kidney cancer mortality. There was an atypically low SMR for total mortality (SMR = 51.3; 95% CI: 49.1–53.6; 2066 deaths) among the land-based workers, suggesting possible selection bias. A detailed review by the authors revealed little evidence of bias. The total SMR for marine vessel workers (SMR = 76.9; 95% CI: 73.9–79.9; 2695 deaths) was more typical of occupational cohort studies. However, analyses of exposure to gasoline using internal comparisons supported the SMR results of no increase in kidney cancer mortality.

Rushton presented results on a study of U.K. refinery ( $n = 34,569$ ) and distribution ( $n = 23,306$ ) workers (45). As the latter are considered to have a greater potential for exposure to gasoline, remarks will be confined to results for these workers. Contrary to an earlier report on this cohort (34), there were no significantly elevated SMRs for kidney cancer among tanker truck drivers. The SMR for kidney cancer was 121 (95% CI: 91–158; 53 deaths) among distribution workers and 141 (95% CI: 91–208; 25 deaths) among tanker truck drivers.

Results from a study of Canadian distribution workers was presented by Schnatter (46). Among all workers, there

was a slight elevation of mortality from kidney cancer (SMR = 1.35; 95% CI: 0.62–2.57; 9 deaths). When restricted to workers with known hydrocarbon exposure the SMR was 1.58 (95% CI: 0.63–3.25). Distribution workers exposed daily to hydrocarbons had a mortality rate twice that of the Canadian population (SMR = 2.08; 95% CI: 0.67–4.85; 5 deaths). Tanker truck drivers had a SMR of 2.10 based on two deaths. Although elevated, none of the risk estimates was statistically significant.

## Discussion

The epidemiologic investigation of a possible link between gasoline exposure and renal cell cancer was initiated by results from a bioassay that found male rats experienced an excess of renal tumors when exposed to vaporized unleaded gasoline, with some suggestion of a dose response (35). In the same study female rats and mice of both sexes showed no association with gasoline. Further experimental research, however, has indicated that the finding in the male rat is due to a unique sex- and species-related protein molecule,  $\alpha_{2u}$ -microglobulin, thereby suggesting that the effect found in the male rat is unlikely to be relevant to humans (47). Nevertheless, as a result of this finding, a number of epidemiologic studies since the mid-1980s have examined gasoline exposure and renal cell cancer risk.

Early nested case-control studies (38,39) among refinery workers and a later industrywide study (43) showed no association between gasoline exposure and renal cancer. Wong et al. (44), in a large cohort study of distribution workers, also found no association. U.K. distribution truckers were found to have a lower, nonsignificant excess risk (SMR = 141) in the current followup (45) than in the earlier report for tanker truck drivers (SMR = 171) (34). Among the industry studies, only Schnatter et al. (46) reported a suggestive association for gasoline exposure. Although all the risk estimates in this study were based on small numbers and compatible with chance, there was some consistency in their findings. Among the nonindustry studies, only the case-control study in Finland had strongly positive or statistically significant results (42). However, the finding was based on a number of occupations not usually considered to be occupationally related to gasoline exposure; for example, 26 of the 39 cases classified as exposed were taxi drivers or drivers of gasoline-powered vehicles. Moreover, after a number of exclusions of subjects and nonresponse, the analysis is based on 338 out of 672 ascertained cases (49%) and 484 out of 1344 identified controls (36%). An analysis of one out of two cases and about one out of three controls raises concern regarding response bias and the possibility that the study subjects used in the analysis are no longer representative of the study base (48).

In summary, the experimental rationale for the initial health concern of gasoline and renal cell cancer appears no longer valid (47), and the weight of the human evidence indicates little likelihood of an association. However, positive findings from recent studies (42,46) suggest that an association between renal cell cancer and gasoline expo-

sure cannot be ruled out at this time. Further research is needed to determine the relation, if any, between gasoline exposure and renal cell cancer.

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