

# Epidemiologic characteristics and risk factors for renal cell cancer

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**Abstract:** Incidence rates of renal cell cancer, which accounts for 85% of kidney cancers, have been rising in the United States and in most European countries for several decades. Family history is associated with a two- to four-fold increase in risk, but the major forms of inherited predisposition together account for less than 4% of renal cell cancers. Cigarette smoking, obesity, and hypertension are the most consistently established risk factors. Analgesics have not been convincingly linked with renal cell cancer risk. A reduced risk of renal cell cancer among statin users has been hypothesized but has not been adequately studied. A possible protective effect of fruit and vegetable consumption is the only moderately consistently reported dietary finding, and, with the exception of a positive association with parity, evidence for a role of hormonal or reproductive factors in the etiology of renal cell cancer in humans is limited. A recent hypothesis that moderate levels of alcohol consumption may be protective for renal cell cancer is not strongly supported by epidemiologic results, which are inconsistent with respect to the categories of alcohol consumption and the amount of alcohol intake reportedly associated with decreased risk. For occupational factors, the weight of the evidence does not provide consistent support for the hypotheses that renal cell cancer may be caused by asbestos, gasoline, or trichloroethylene exposure. The established determinants of renal cell cancer, cigarette smoking, obesity, and hypertension, account for less than half of these cancers. Novel epidemiologic approaches, including evaluation of gene–environment interactions and epigenetic mechanisms of inherited and acquired increased risk, are needed to explain the increasing incidence of renal cell cancer.

**Keywords:** renal cell cancer, epidemiology, risk factor, review

## Descriptive epidemiology

Kidney cancer is the ninth most common cancer in developed countries.<sup>1</sup> Approximately 85% of kidney cancers are renal parenchyma (renal cell) cancers, while the remainder for the most part are urothelial cancers of the renal pelvis.<sup>2</sup> Approximately 80% of renal cell cancers are clear cell adenocarcinomas, the remainder being papillary (~15%), chromophobe (~5%), and collecting duct carcinomas (<1%). Both renal cell and renal pelvis cancers are about twice as common among men as among women,<sup>1–3</sup> with the mean age at diagnosis in the early 60s for renal cell cancer and in the late 60s for renal pelvis cancer. For renal pelvis cancer, there is a strong tendency to develop multiple transitional epithelial tumors, particularly in the urinary bladder and ureter.<sup>4</sup> For the most part, renal pelvis cancer parallels bladder cancer in epidemiologic characteristics and risk factors and has been addressed by the authors elsewhere.<sup>4</sup>

Rates of renal cell cancer vary internationally as much as 10-fold (Table 1), suggesting a strong role for exogenous risk factors in addition to possible roles of geographic differences in genetic susceptibility and diagnostic variability. Incidence is generally highest in several Western and Eastern European countries, as well as in parts of Italy, in North America, and in Australia/New Zealand. The lowest rates are reported in Asia and Africa. How much of this difference is a function of completeness of reporting by country is not clear, but it probably plays a important role.

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**Table 1** International variation in age-adjusted incidence rates (per 100,000 person-years) for renal cell cancer in selected countries

Country	Male	Female
Czech Republic	20	10.2
France, Bas-Rhin	15.6	7.3
Iceland	14.8	7.3
Estonia	14.1	7.9
Italy, Florence	13.7	6.6
Slovakia	12.5	5.8
Poland, Warsaw	12.2	5.9
US SEER: black	12.1	6.4
Italy, Venezia	11.7	5
Germany, Saarland	11.4	6.2
Israel, Jews	11.2	6.1
Finland	11	6.2
Poland, Lower Silesia	10.1	5.7
US SEER: white	9.6	4.9
Canada	9.5	5.2
Australia, New South Wales	8.7	4.6
New Zealand	8.6	4.5
France, Isere	8.3	3.9
Netherlands	8.2	4.6
Norway	8	4.6
Scotland	7.9	4.3
Sweden	7.8	4.8
Denmark	7.4	4.1
UK, England	6.7	3.3
Seoul, Korea	4.5	1.9
Japan, Osaka	4.4	1.5
China, Taiwan	3.6	2.6
Columbia, Cali	2.9	2.3
China, Shanghai	2.6	1.5
Israel, non-Jews	2.5	1.9
Zimbabwe	1.1	1.6
Uganda	1	1.1

**Note:** Data obtained from Parkin and colleagues.<sup>1</sup>

Over the past several decades, incidence rates for renal cell cancer have been rising steadily each year in Europe and the United States,<sup>5</sup> although incidence rates appear to have recently stabilized or decreased in many European countries.<sup>6</sup> In the United States in 2008, 54,390 new cases and 13,010 deaths were expected from kidney cancer.<sup>2</sup> A recent report showed that, while the rate of new cancer diagnoses overall dropped 1.8% among men and 0.5% among women in the United States between 2001 and 2005, kidney cancer incidence rose 1.7% per year for males and 2.2% per year for females.<sup>7</sup> While there has been a decrease in the size of diagnosed renal

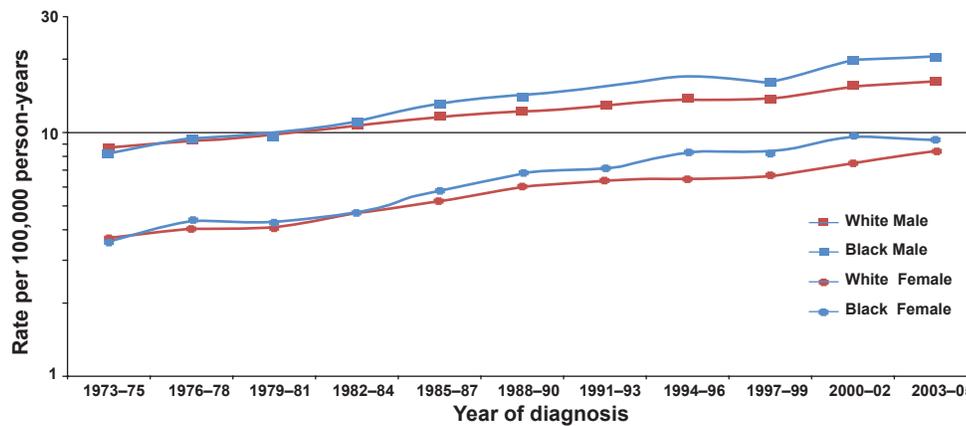
cell tumors over time,<sup>8,9</sup> as a result of rapidly improved imaging technology and earlier detection over the last 25 years, an increasing incidence of large and late-stage renal cell cancers has also been observed and accounts in part for the overall increase in incidence.<sup>5,9,10</sup> In the United States, increases in incidence have been more rapid among women than men<sup>11</sup> and, in particular, among blacks than whites,<sup>10</sup> leading to a substantial shift in excess from among whites to among blacks,<sup>10</sup> which is becoming pronounced over time (Figure 1). Age-adjusted incidence rates of renal cell cancer among white men, white women, black men and black women in the United States during 2000–2005 were, respectively, 16.31, 8.03, 19.24, and 8.87 per 100,000 person-years<sup>3</sup> (Table 2).

Five-year relative survival rates for renal cell cancer in the United States reached 65.1% among men and 66.8% among women by 2005,<sup>3</sup> compared with below 40% in the early 1960s<sup>10</sup> (Table 3). For localized renal cell cancer cases, the five-year relative survival rate is approximately 90%, regardless of race or gender.<sup>3</sup> In Europe, kidney cancer mortality peaked in the early 1990s at 4.8 per 100,000 in men and 2.1 per 100,000 in women, and then declined to 4.1 and 1.8 per 100,000, respectively, by 2004.<sup>6</sup> Despite increasing incidence rates, United States kidney cancer mortality rates, which are based on deaths from renal cell cancer as well as cancer of the renal pelvis, have been remarkably stable over the past 15 years, fluctuating between 4.1 and 4.3 per 100,000, suggesting a benefit of early detection and consequent surgical treatment.

## Risk factors for renal cell cancer

Epidemiologic studies for consideration in this review were identified through a MEDLINE® search of the literature. For the purposes of this review, all papers published through 2008 were identified by use of either the term “renal cancer” or the term “kidney cancer” together with the term “risk factor” or “epidemiology.” Moreover, all review papers addressing risk factors for kidney cancer in general or renal cell cancer in particular were identified, and references were examined to supplement, if necessary, papers recovered through the initial search. Findings of individual studies were evaluated, and a qualitative summary of the results is presented herein. In the interest of keeping the paper to a reasonable length, we have not attempted to cite every paper that we identified, but rather to emphasize those findings that reflect consistency in the literature.

Information on risk factors for renal cell cancer was established by a large number of case-control studies starting in the 1980s and supported more recently by cohort studies.<sup>12–71</sup> The largest case-control study to date, based on 1,732 cases and



**Figure 1** Trends in age-adjusted (2000 United States standard) incidence of renal cell cancer by race and sex, 1973–2005 (Based on SEER data for nine geographic regions of the United States: Atlanta, Georgia; Connecticut; Detroit, Michigan; Hawaii; Iowa; New Mexico; San Francisco/Oakland, California; Seattle/Puget Sound, Washington; and Utah).<sup>3</sup>

2,309 controls, was a multicenter collaborative investigation conducted in five countries using a common protocol, questionnaire, field procedures, and analytic techniques.<sup>34,72–78</sup> When citing results from this international collaborative investigation, only the combined multicenter results will be reported, not center-specific findings.

## Genetic susceptibility

Renal cell cancer occurs in both sporadic and hereditary forms. Having a first degree relative with kidney cancer has been associated with a two- to four-fold increased risk in most studies.<sup>79</sup> Hereditary renal cell cancer tends to occur earlier in life than sporadic forms of the disease, and often involves bilateral, multifocal tumors.<sup>80</sup>

Although only about 3%–4% of renal cell cancers are explained by inherited predisposition,<sup>80,81</sup> it is surprising that no cancer has as many different types of genetic predisposition as renal cell cancer.<sup>82</sup> Among the rare high-penetrance

genetic forms of renal cell cancer are von Hippel–Lindau (VHL) disease (predisposing to clear cell cancer), hereditary papillary carcinoma, hereditary leiomyomatosis and renal cell cancer (papillary), Birt–Hogg–Dubé syndrome (mainly chromophobe and oncocytoma), chromosome 3 translocation-associated (clear cell), tuberous sclerosis (clear cell), and a mutated succinate dehydrogenase (SDHB) gene.<sup>80,81</sup> In contrast, the only hereditary syndrome with known predisposition to renal pelvis cancer is hereditary nonpolyposis colorectal cancer.<sup>80</sup> Genetics play a role in renal cell cancer beyond clearly inherited susceptibility, as it has been shown that the majority of noninherited clear cell carcinomas are associated with inactivation of the *VHL* gene through mutation or promoter hypermethylation.<sup>80</sup>

## Obesity

Renal cell carcinoma is consistently associated with obesity in virtually all epidemiologic studies, including recent large

**Table 2** Age-adjusted incidence rates\* for renal parenchyma cancer by racial/ethnic group and sex according to SEER program, 2000 through 2005

	No. male	(Rate)	No. female	(Rate)
White	26,195	16.31	15,345	8.03
Black	3,115	19.24	1,884	8.87
Asian	1,258	7.80	731	3.67
American Indian	225	12.58	159	7.67
White non-Hispanic	22,947	16.43	13,232	7.96
White Hispanic	3,248	15.81	2,113	8.65

**Notes:** \*Per 100,000 person-years, age-adjusted using 2000 United States standard population. Data sourced from SEER Program 17 Registries population, representing 26% of the United States population.<sup>3</sup>

**Table 3** Five-year relative and cause-specific survival rates\* for renal parenchyma cancer by race and sex according to SEER program for cases diagnosed from 1990 through 2004

	% Male	% Female
<i>Relative survival</i>		
White	65.1	66.8
Black	60.0	65.0
<i>Cause-specific survival</i>		
White	67.7	69.6
Black	70.5	71.7

**Notes:** \*Percentage of cases surviving five years after diagnosis of a first primary cancer in the renal parenchyma. Data sourced from SEER Program 17 Registries Population, representing 26% of the United States population.<sup>3</sup>

prospective studies in the Netherlands, Norway, and the United States.<sup>59,60,62,65,70,71,78,83–85</sup> Most studies have found an association with elevated body mass index (BMI) among both men and women, and abdominal obesity, as indicated by waist-to-hip ratio,<sup>58,65,70,71,85</sup> may play an important role in this association, particularly among women. A quantitative review of the published literature reported a summary relative risk for renal cell cancer of 1.07 per unit increase of BMI.<sup>83</sup> A more recent meta-analysis reported that associations with increased BMI were stronger in women than in men; summary risk ratios per 5 kg/m<sup>2</sup> increase in BMI were 1.24 (95% confidence interval [CI] 1.15–1.34) among men and 1.34 (95% CI 1.25–1.43) among women.<sup>86</sup>

Several plausible mechanisms have been suggested for the association between obesity and renal cell cancer, but the actual mechanism remains speculative. Obesity may promote changes in circulating levels of estrogen and other steroid hormones, or elevated levels of insulin-like growth factor-I (IGF-I), which could in turn contribute to the development of renal cell cancer.<sup>87–90</sup> Lipid peroxidation, which is increased among obese subjects, has been hypothesized to be partly responsible for the association of obesity with renal cell cancer through the formation of DNA adducts.<sup>91</sup> Other conjectured mechanisms include elevated cholesterol level and down-regulation of low-density lipoprotein receptor, lower levels of vitamin D, and increases in adipose tissue-derived hormones and cytokines, such as leptin and adiponectin.<sup>84,92,93</sup>

The increasing prevalence of obesity, rapidly becoming a worldwide epidemic,<sup>93–95</sup> is likely to account in part for the rising incidence of renal cell cancer. Recent calculations suggest the proportion of renal cell cancer attributable to being overweight and obese could be as high as 40% in the United States and Canada and 30% in Europe.<sup>83,87,93,96,97</sup>

## Cigarette smoking

Cigarette smoking is a recognized though moderate cause of renal cell cancer.<sup>98</sup> A recent meta-analysis<sup>99</sup> of data from 19 case-control studies (8,032 cases and 13,800 controls) and five cohort studies (1,457,754 participants with 1,326 renal cell cancer cases) reports statistically significant relative risks of 1.5 and 1.2 for male and female smokers, respectively. There was a strong dose-dependent increase in risk, up to 2- and 1.6-fold among heavy (21 or more cigarettes per day) men and women smokers, respectively. There was a significant decline in risk in both sexes with years of cessation, with a 15% to 30% reduction in risk 10 to 15 years after quitting.<sup>99</sup> Approximately 20% to 30% of renal cell cancers among

men and 10% to 20% among women are estimated to be attributable to cigarette smoking.<sup>34,100,101</sup>

## Hypertension and antihypertensive medications

The recent increases in renal cell cancer incidence may be associated, again in an unknown way, with the increasing prevalence of hypertension in the United States, particularly among blacks and among women.<sup>101,102</sup> While it is difficult to separate the effects of hypertension or its treatment on renal cell cancer risk, as they are highly correlated variables, the collective epidemiologic evidence to date suggests that it is hypertension itself that is the determinant. Most studies have reported risks for renal cell cancer associated with either recorded blood pressure or reported hypertension ranging between 1.2 and 2 or greater,<sup>48,51,54–56,62,68,69,72,103–106</sup> although not all of the studies were able to adjust for the effect of antihypertensive medications. Dose-response relations between measured blood pressure level and renal cell cancer risk have been reported,<sup>54,56,106</sup> although only one of these studies provided data on women and considered the effect of antihypertensive medication.<sup>106</sup> In that analysis of 254,935 men and women in the European Prospective Investigation into Cancer and Nutrition (EPIC), the relative risks for the highest versus the lowest category of systolic ( $\geq 160$  vs  $< 120$  mmHg) and diastolic ( $\geq 100$  vs  $< 80$  mmHg) blood pressure were 2.48 (95% CI 1.53–4.02) and 2.34 (95% CI 1.54–3.55), respectively, independent of use of antihypertensive medication. A case-control study reported that high systolic and diastolic blood pressures were independently associated with increased renal cell cancer risk in both sexes when analyses were restricted to those who never took antihypertensive medication.<sup>103</sup> Several<sup>55–57,63,106</sup> cohort studies have demonstrated an increased risk even after exclusion of the early years of follow-up, when early stage, prediagnostic renal tumors may themselves lead to elevated blood pressure. Recent findings from the Netherlands cohort study<sup>105</sup> suggest that the association with hypertension may be stronger among the small fraction of sporadic renal cell cancer patients with von Hippel–Lindau gene mutations, but this needs to be confirmed in future studies.

Most epidemiologic studies of antihypertensive drugs and renal cell cancer risk have found that diuretic use, a causal factor candidate in early studies, is not an independent risk factor, and adjustment for high blood pressure appears to eliminate any excess risk associated with diuretic use.<sup>48,62,72,103</sup> In a study of the various classes of antihypertensive medications, no particular type or class of

these medications was consistently associated with renal cell cancer risk.<sup>107</sup>

The biologic mechanism for the association between high blood pressure and renal cell cancer risk is unknown. Among the candidate hypotheses regarding mechanism has been hypertension-induced renal injury and metabolic or functional changes within the renal tubule induced by hypertension increasing susceptibility to carcinogens. It has also been speculated that elevated levels of IGF-I or lipid peroxidation associated with hypertension, as well as up-regulation of hypoxia-inducible factors, could contribute to the development of renal cell cancer. Contrary to expectation, detection bias due to incidental diagnosis during work-ups for hypertension was not supported in a study which directly evaluated that hypothesis.<sup>108</sup>

## Analgesics

Historically, the causal connection of heavy use and abuse of phenacetin-containing analgesics and transitional cell cancers of the renal pelvis has long been recognized. Phenacetin's effect on adenocarcinomas of the renal parenchyma, however, is inconclusive,<sup>27,28,109</sup> and it is now impossible to assess because phenacetin-containing analgesics have been off the market for up to 30 years in most countries and reliable recall of past intake is no longer achievable.

Among other analgesics, acetaminophen has received the most attention, since it is the major metabolite of phenacetin, although several studies have also examined the effect of aspirin use on renal cell cancer.<sup>21,73,109-113</sup> Neither acetaminophen nor aspirin has been credibly associated with an increase in renal cell cancer risk.<sup>73,111</sup>

## Statins

Statins are widely used drugs for the treatment of lipid disorders, particularly hypercholesterolemia. Despite reported antitumorigenic activity of statins, including their inhibition of proliferation and promotion of apoptosis, their potential effectiveness for the primary prevention of cancer remains to be reliably demonstrated. While some observational studies have reported inverse associations with cancer, neither the Cholesterol Treatment Trialists' (CTT) Collaboration<sup>114</sup> nor two recent meta-analyses<sup>115,116</sup> found evidence of an effect of statin therapy on cancer risk. A study based on Veteran Affairs (VA) databases in the United States reported a 50% reduced risk of renal cell carcinoma among statin users compared with nonusers.<sup>117</sup> This finding may be influenced by selection bias, however, since the controls were drawn from frequent users of the VA system who might be more likely to

be prescribed statins. Furthermore, the study did not address the influence of dose, duration, and type of statin in relation to renal cell cancer risk. There is some evidence that only lipophilic statins, such as simvastatin and lovastatin, possess antineoplastic effects, whereas hydrophilic statins, such as pravastatin, do not have chemopreventive potential.<sup>118,119</sup> Other epidemiological studies reporting on the association of statin use and urologic cancers have yielded inconsistent results,<sup>119-125</sup> however, only combined results for kidney and bladder cancer were presented in many of these studies. A follow-up study of 361,859 statin users, most of whom received lovastatin or simvastatin, found a non-significantly increased risk of kidney/renal pelvis cancer.<sup>125</sup> Two case-control studies reported no association between current or regular statin use and kidney cancer.<sup>121,123</sup> Most published studies on statin use had relatively short follow-up and reported for the most part only on the most common cancer types. Further research is warranted to investigate the association between use of statins and any potential increase or decrease in risk of renal cell cancer, with particular focus on duration, intensity, and type and dose of statin used.

## Dietary factors

Renal cell cancer has not been convincingly linked to any specific dietary factor, with the exception of a moderately consistent protective effect for overall fruit and vegetable consumption.<sup>61,126-130</sup> However, two recent large prospective studies, one based on 375,851 participants in the EPIC study<sup>131</sup> and the other based on 120,852 men and women in the Netherlands Cohort Study on Diet and Cancer (NLCS),<sup>132</sup> reported no protective effect of vegetable and/or fruit consumption on renal cell cancer. Some epidemiologic studies suggest that elevated protein consumption may be a risk factor for renal cell cancer. There may be some biologic plausibility to a high protein diet affecting risk of renal cell cancer, because animal studies have shown protein intake can induce renal tubular hypertrophy, but the largest study to date to evaluate this association failed to provide clear support for this hypothesis,<sup>78</sup> as has a large, pooled analysis of 13 cohort studies.<sup>133</sup>

Elevated risks have been reported for consumption of meat,<sup>16,24,27,28,47,128</sup> milk,<sup>21,25</sup> and margarine, oils and other fat types,<sup>25,47</sup> however, most of these findings were not adjusted for confounding by energy intake. Sporadic inverse associations have been reported with respect to vitamin C,<sup>47</sup> Vitamin E,<sup>78,128</sup> carotenoids,<sup>127</sup> and calcium,<sup>128</sup> but no particular micronutrient or vitamin has been consistently observed to decrease or increase the risk of renal cell cancer in case-control

or cohort studies. Although originally thought almost 30 years ago to be a key area for renal cell cancer causation, dietary studies have not fulfilled their early promise.

## Alcohol consumption

Early ecologic studies consistently suggested a positive correlation between kidney cancer and per capita consumption of alcohol.<sup>134–136</sup> However, these ecologic findings were not confirmed by numerous analytic epidemiologic studies of renal cell cancer conducted during the ensuing two decades.<sup>4,66</sup> After adjustment for the confounding effect of cigarette use, virtually all studies showed no association between alcohol consumption and renal cell cancer.<sup>16–20,24,25,27,28,30,78</sup> Cohort studies of alcoholics and brewery workers have also reported no excess of mortality from kidney cancer.<sup>137–142</sup>

By contrast, a *post hoc* hypothesis has recently appeared in the literature that moderate levels of alcohol consumption may be protective for renal cell cancer. The findings of recent individual studies show considerable heterogeneity and inconsistency with respect to the categories of alcohol consumption, the amount of alcohol intake reportedly associated with decreased renal cell cancer risk, and differential observations between men and women. A pooled analysis of data from 12 prospective studies of renal cell cancer was recently published, based on results of five published studies<sup>58,143–145</sup> as well as numerous others which had not previously published their data related to alcohol consumption.<sup>146</sup> The pooled analysis was based on 1430 incident cases of renal cell cancer (719 men and 711 women), and demonstrated an apparent inverse-response relation at levels of consumption equivalent to less than a drink per day, with no further protective effect at levels of intake above a drink a day. It is difficult to speculate what biologic mechanism could explain this type of dose-response pattern, unless of course one invokes a hormesis-like effect of low-dose alcohol on renal cancer risk while other organs seemingly do not enjoy this anticarcinogenic effect.

Finally, alcohol itself is a known human carcinogen and heavy alcohol drinking has been conclusively linked to increased risks of numerous types of cancer, including oral, pharyngeal, laryngeal, esophageal, liver and probably breast and colon and rectum.<sup>147</sup> A protective effect of alcohol consumption on renal cell cancer at very low levels of intake has little biologic plausibility or face validity. In addition to the extensive analytic epidemiologic evidence from the past 40 years, the descriptive patterns of renal cell carcinoma are not consistent with an inverse association with alcohol intake. In particular, the rate of renal cell carcinoma among

men is twice that among women worldwide, whereas men tend to consume alcohol at substantially higher levels than women.

## Hormonal and reproductive factors

Reductions in risk of renal cell cancer have been reported among users of oral contraceptives in some,<sup>76,148</sup> but not all studies,<sup>149,150</sup> and in the large international case-control study protection was restricted to nonsmokers.<sup>76</sup> Several studies have reported an almost two-fold increased risk among women with high parity compared with nulliparous women, after adjustment for obesity,<sup>76,148,151</sup> and an inverse association between age at first birth and risk of renal cell cancer has been reported in some<sup>28,39,149,151</sup> but not all studies.<sup>148,150</sup> Hormones have induced renal tumors in laboratory animals; however, with the exception of a positive association with parity, evidence for a role of hormonal or reproductive factors in the etiology of renal cell cancer in humans is limited and not entirely consistent to date.

## Occupation

As compared with bladder cancer, renal cell cancer has not been convincingly linked to any occupational exposure.<sup>4</sup> However, because of the large number of epidemiologic studies, particularly case-control studies, that have been conducted over the last three decades, a number of sporadic associations have been reported between exposures or jobs/industries and renal cell cancer. Asbestos has been associated with elevated renal cancer mortality in two cohort studies, one of insulators<sup>152</sup> and one of asbestos products workers,<sup>153</sup> as has self-reported asbestos exposure in several case-control studies, including the large international study.<sup>75</sup> An extensive meta-analysis of occupational cohort studies of asbestos-exposed workers showed little relation to increased risk for renal cancer.<sup>154</sup>

In the early 1980s, unleaded gasoline was suspected as a risk factor for renal cell cancer based on long-term rodent bioassays in which male rats developed renal tumors. Since then, a number of occupational cohort and nested case-control studies have examined the effect of gasoline exposure in numerous populations, and the collective evidence to date does not support a relation between gasoline and risk of renal cell cancer.<sup>155–165</sup> Further, the mechanism by which male rats developed kidney cancer when exposed to unleaded gasoline vapors, via a unique protein molecule, alpha2 microglobulin, has no counterpart in humans.<sup>156,166</sup>

In recent years, considerable attention has focused on the solvent trichloroethylene (TCE), largely as a result of

animal findings and of three epidemiologic studies conducted in one area of Germany, initiated in response to a cluster of renal cell cancer cases observed in a plant. All three of these studies reported strikingly elevated relative risks for renal cell cancer associated with TCE exposure.<sup>167–169</sup> The findings contrast starkly with results from other investigations, and several serious methodological shortcomings of these studies have been noted,<sup>170–172</sup> limiting any conclusion that can be drawn. To date, seven occupational cohort studies have evaluated the relationship between TCE exposure and specific types of cancer. The two largest employed sophisticated methods of exposure assessment and both internal and external comparisons.<sup>173,174</sup> Neither of these studies reported a significantly increased risk of renal cell cancer among TCE-exposed workers. The most recent cohort study,<sup>175</sup> conducted in Denmark, evaluated cancer incidence among 40,049 workers with presumed TCE exposure and found a weak association with renal cell cancer among those thought to be heavily exposed to TCE. The weight of the evidence to date, however, does not provide consistent, credible support for the hypothesis that TCE is a cause of renal cell cancer in humans.<sup>176</sup> Whether TCE is a renal carcinogen in humans remains an open question, which will require more and better research.

A German study reported that *VHL* mutations were found in 33 of 44 RCC patients from North Rhine–Westphalia with TCE exposure.<sup>177,178</sup> Of the 33 patients with *VHL* mutations, 14 had multiple *VHL* mutations and remarkably, 13 had the same C to T substitution in codon 81.<sup>177</sup> Two subsequent studies could not confirm either the tendency towards multiple *VHL* mutations or the *VHL* codon 81 mutation hot spot in TCE-exposed RCC patients from Germany and France.<sup>179,180</sup> In view of the widespread use of TCE around the world, it is noteworthy that among approximately 600 *VHL* mutations reported in sporadic RCC patients from other published studies (predominately of western European patients), only one other C to T substitution in codon 81 has been reported.<sup>181</sup> This suggests that the *VHL* mutation hot spot in the German study resulted from either a unique TCE exposure situation in a restricted geographic area or some other environmental exposure prevalent in that geographic area. If the *VHL* codon 81 mutation hot spot is a marker for TCE-induced RCC, then the overall findings suggest that TCE is not a major contributor to the global RCC burden.

## Kidney transplantation and dialysis

Acquired renal cystic disease of the native kidneys is believed to account for the substantially higher average

annual incidence of renal cell carcinoma in dialysis patients, independent of patient age or underlying renal disease.<sup>182,183</sup> Several recent studies of cancer risk subsequent to kidney transplantation have found a substantially increased risk of acquired renal cystic disease and renal cell cancer compared with the general population, presumed to be a result of immune-suppressing medications used in transplant patients.<sup>184</sup>

## Summary

To date, the causal determinants identified for renal cell cancer in epidemiologic studies, cigarette smoking, obesity, and hypertension, are at best moderate in their effect on risk and account for less than half of these cancers. Major, explanatory causes of renal cell cancer await novel epidemiologic approaches, including more sophisticated genetic studies. Because single-gene determinants of renal cell cancer have been thoroughly investigated for almost 30 years with at best very limited success, future investigations should examine more complex genetic associations, including gene-environment interactions and epigenetic mechanisms of inherited and acquired increased risk.

## Acknowledgments

This paper is dedicated to the memory of Dr Edward Lipworth (1910–2009) a leading urologist in both South Africa and Israel whose lifelong passion for learning and helping mankind extended almost an entire century.

## Disclosure

The authors report no conflicts of interest in this work.

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