The Epidemiology of Renal Cell Carcinoma

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Purpose: We identified and examined risk factors for renal cell cancer, some of which may explain in part the trends of steadily increasing incidence rates, particularly in black Americans.

Materials and Methods: Epidemiological studies were identified through a MEDLINE® search of the literature through February 2006. A qualitative summary of the results of individual studies is presented.

Results: Cigarette smoking and obesity are the most consistently established causal risk factors, accounting for about 20% and 30% of renal cell cancers, respectively. Hypertension appears to independently influence renal cell cancer risk. Neither acetaminophen nor other analgesics have been convincingly linked with renal cell cancer. With respect to diet a general protective effect of fruit and vegetable consumption is the only consistently reported finding. For occupational factors the weight of the evidence provides no consistent support for the hypotheses that renal cell cancer may be caused by asbestos, gasoline or trichloroethylene exposure. Self-reported family history is associated with 2 to 3-fold increases in risk and the major inherited forms of renal cell cancer together account for about 2% of this malignancy.

Conclusions: A further reduction in cigarette smoking, and a decrease in the rates of obesity and hypertension would likely moderate the increasing incidence of renal cell cancer. Epidemiological studies, including evaluation of gene-environment interactions, are needed to specifically identify reasons for the increasing incidence, particularly for assessing the roles of obesity and hypertension. Special attention should be focused on black Americans since their incidence rate recently increased to significantly surpass that in white Americans.

Key Words: kidney; kidney neoplasms; carcinoma, renal cell; epidemiology; risk factors

Kidney cancer accounts for about 2% of all new cancer cases worldwide[1] with 38,890 cases and 12,840 deaths expected in 2006 in the United States.[2] Renal parenchyma (renal cell) cancer accounts for about 85% of kidney cancers diagnosed in the United States from 1992 through 2002, while the remainder was composed mainly of renal pelvis cancer (approximately 12%) and other rare malignancies (approximately 2%).[3] Virtually all renal cell cancers are adenocarcinomas, while the majority of cancers of the renal pelvis are transitional cell carcinomas. In this review for the most part we emphasize results for renal cell cancer because it is the predominant form of kidney cancer and it is increasing in incidence.

DEMOGRAPHIC PATTERNS

Renal cell cancer occurs about twice as often in men as in women.[1] Average age at diagnosis is in the early 60s (fig. 1). Incidence rates for renal cell cancer have been increasing steadily each year in Europe and the United States in the last 3 decades (fig. 2).[4] This increase cannot be entirely accounted for by improved imaging modalities since an increasing incidence of late stage renal cell cancers has also been observed.[4,5] Furthermore, rates have increased, although the number of unsuspected renal cell cancers detected only at autopsy has decreased due to decreasing autopsy rates.[6] Increases in incidence have been more rapid in females than males[7] and in black than white individuals,[5] leading to a substantial shift in excess from white to black individuals,[5] which is becoming more pronounced with time. Age adjusted incidence rates of renal cell carcinoma in white men, white women, black men and black women in the United States during 1992 to 2002 were 13.8, 6.6, 16.8 and 8.0/100,000 person-years, respectively (table 1).

The incidence of cancer of the renal pelvis has decreased slightly in white men in the last 3 decades, while rates in white women and black individuals have remained relatively stable (data not shown).[4] Age adjusted incidence rates in white men, white women, black men and black women in the United States during 1992 to 2002 were 1.66, 0.90, 1.18 and 0.68/100,000 person-years, respectively (table 1).

The prognosis in patients diagnosed with renal cell cancer has slowly improved with time with 5-year relative survival rates as high as 64% by 2002 compared with less than 40% in the early 1960s (table 2).[5] A similar increase in 5-year relative survival has not been observed for cancer of the renal pelvis, for which rates are lower, particularly in women (table 2). However, relative survival is likely to underestimate the true survival rate for renal pelvis cancer since the average patients with renal pelvis cancer are heavy smokers who are also at high risk for many other causes of death. In fact, when calculating cause specific survival instead, ie the probability of a patient with kidney cancer dying with kidney cancer as the cause of death, the survival rates for renal cell and renal pelvis cancer are more

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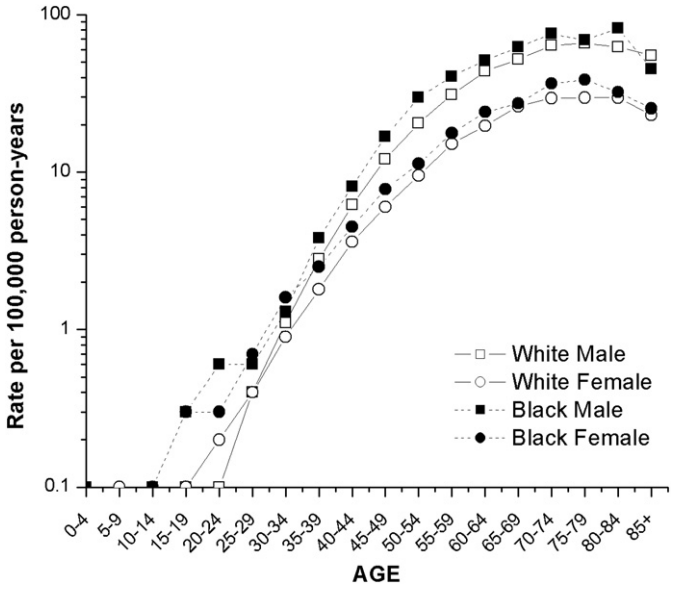

FIG. 1. Age specific incidence of renal cell cancer in United States by race and sex in 1992 to 2002 based on SEER data for 13 geographic regions of United States, including Atlanta, Georgia; Connecticut; Detroit, Michigan; Hawaii; Iowa; Los Angeles County, California; New Mexico; San Francisco/Oakland and San Jose/Monterey, California; Seattle/Puget Sound, Washington; Utah; rural Georgia; and Alaska natives.[3]

similar (table 2). In the United States and Europe kidney cancer mortality rates, which have not been partitioned by kidney subsite and are based on deaths from renal pelvis cancer along with those from cancer of the renal parenchyma, increased until the middle 1990s, after which the rates stabilized (fig. 3).[8]

Rates of renal cell cancer vary internationally more than 10-fold, suggesting a strong role for exogenous risk factors,

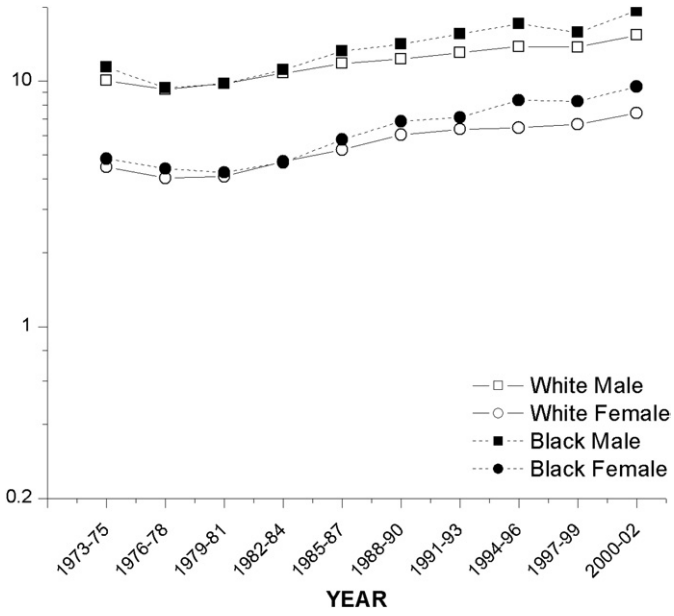

FIG. 2. Trends in 2000 United States standard age adjusted incidence of renal cell cancer by race and sex in 1973 to 2002 based on SEER data for 9 geographic regions of United States, including Atlanta, Georgia; Connecticut; Detroit, Michigan; Hawaii; Iowa; New Mexico; San Francisco/Oakland, California; Seattle/Puget Sound, Washington; and Utah.[3]

TABLE 1. *Incidence rates* for renal parenchyma and renal pelvis cancer by racial/ethnic group and sex according to SEER program in 1992 to 2002*[3]

	No. Males	(rate)	No. Females	(rate)
Renal parenchyma:				
White	18,489	13.77	10,908	6.60
Black	2,296	16.77	1,465	7.95
Asian	1,195	7.30	651	3.29
American Indian	212	14.66	133	7.33
White nonHispanic	16,384	13.79	9,568	6.56
White Hispanic	2,076	13.44	1,320	6.89
Renal pelvis:				
White	2,104	1.66	1,563	0.90
Black	150	1.18	118	0.68
Asian	164	1.13	103	0.56
American Indian	7	0.42	5	0.30
White nonHispanic	1,936	1.70	1,435	0.91
White Hispanic	165	1.37	123	0.74

* Per 100,000 person-years, age adjusted using 2000 United States standard.

in addition to possible roles of geographic differences in genetic susceptibility and diagnostic variability. The incidence is generally highest in several Western and Eastern European countries as well as in parts of Italy, in North America and in Australia/Zealand. The lowest rates are reported in Asia and Africa.[1]

MATERIALS AND METHODS

Epidemiological studies for consideration in this review were identified through a MEDLINE® search of the literature. Our previously published review of the epidemiology of renal cell cancer included all studies published through 1999.[9] For the purposes of this updated review all articles published from 1999 through 2006 were identified by the term renal cancer or the term kidney cancer together with the term risk factor or epidemiology. Moreover, all review articles addressing risk factors for kidney cancer in general or renal cell cancer in particular were identified and, if necessary, references were examined to supplement studies recovered through the initial search. Findings of individual studies were evaluated and a qualitative summary of the results is presented. In the interest of keeping our review to a reasonable length and within the limitations set by the Journal of Urology® we have not attempted to cite every

TABLE 2. *Five-year relative and cause specific survival rates for renal parenchyma and renal pelvis cancer by race and sex according to SEER program in 1992 to 2002*[3]

	% Males	% Females
	Relative survival	
Renal parenchyma:		
Whites	64.2	64.8
Blacks	58.6	63.0
Renal pelvis:		
Whites	58.2	47.9
Blacks	61.3	48.1
	Cause specific survival	
Renal parenchyma:		
Whites	65.9	67.8
Blacks	69.0	70.4
Renal pelvis:		
Whites	68.5	59.4
Blacks	69.0	72.0

Survival rates 5 years following diagnosis of first primary cancer in the renal parenchyma or renal pelvis.

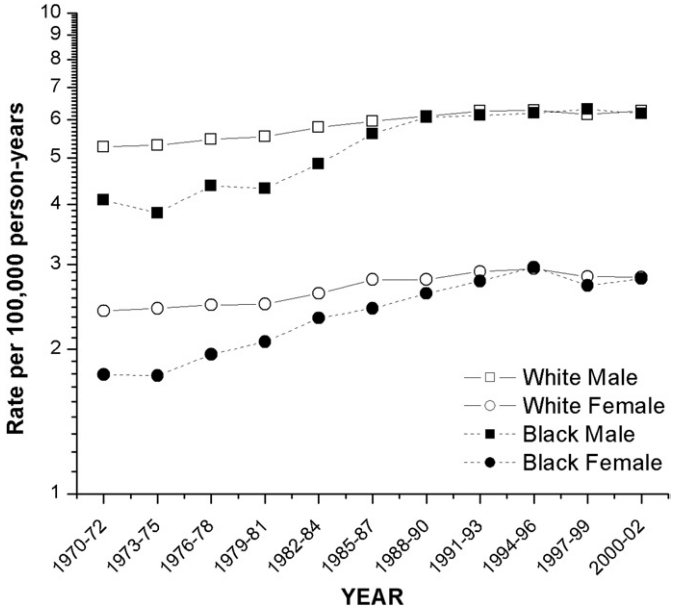

FIG. 3. Trends in 2000 standard age adjusted mortality from kidney cancer by race and sex in 1969 to 2002 based on National Center for Health Statistics data for entire United States.[3]

study that we identified. Rather, we emphasize findings that reflect consistency in the literature.

Virtually all information on risk factors for renal cell cancer comes from a large number of case-control studies performed in many countries, including the United States, Canada, England, Australia, Italy, Finland, France, Denmark, Sweden and China, although in the last few years the results of a number of cohort studies have been published. The largest and most comprehensive study to date, based on 1,732 cases and 2,309 controls, was a multicenter investigation performed in 5 countries using a common protocol, questionnaire and field procedures.[10–17] Although groups at individual study centers participating in this international study have reported center specific results, throughout this review only the combined multicenter results are reported.

Renal cell cancer and renal pelvis cancer generally reflect different risk factor patterns. Since the overwhelming risk factor for renal pelvis cancer is cigarette smoking and in the past the abuse of analgesics containing phenacetin, we have limited the risk factor review to studies that focus specifically on renal cell cancer.

Renal cell cancer occurs in sporadic and familial forms. Having a first degree relative with kidney cancer has been associated with a 2 to 3-fold increased risk in most studies.[18] Few cancers have as many different types of genetic predisposition as renal cell cancer, although to date only about 2% of renal cell cancer cases can be explained by genetic predisposition. Due to the extensive literature on genetics and renal cell cancer[19–21] the area was not addressed in this review of exogenous risk factors.

RISK FACTORS

Socioeconomic Factors

The generally higher mortality and incidence rates for kidney cancer in urban than in rural areas[1] is apparent primarily in men. It probably reflects history of cigarette smoking as well as the greater availability of medical care and imaging technology in urban than in rural areas. In general no consistent association has been demonstrated between renal cell cancer and social class variables, such as education or income.

Cigarette Smoking

Cigarette smoking is the most consistently established causal risk factor for renal cell cancer.[9] It has been estimated to account for approximately 20% to 30% of renal cell cancers in men and 10% to 20% in women.[9,10] A recent meta-analysis, which pooled data from 19 case-control studies based on 8,032 cases and 13,800 controls, and 5 cohort studies based on 1,457,754 participants with 1,326 renal cell cancer cases, revealed a relative risk of 1.54 and 1.22 in male and female smokers, respectively.[22] There was a strong dose dependent increase in risk, with a relative risk of 2.03 in heavy male smokers and 1.58 in heavy female smokers with heavy smoking defined as 21 or more cigarettes daily. Renal cell cancer risk associated with cigarette smoking has been shown to decrease significantly with years of cessation in men and women, with a 15% to 30% decrease in risk after 10 to 15 years of quitting.[22]

Obesity

Obesity has been linked to an excess risk of renal cell cancer in virtually every case-control and cohort study that has examined this relation. A few early studies showed the association primarily in women but most studies have demonstrated an effect of increased body mass index that is equally strong in men and women.[17,23,24] A recent quantitative review of the published literature indicated a summary relative risk for renal cell cancer of 1.07/U increase in body mass index.[23] This estimate is remarkably consistent with that in a recent prospective study based on 2 million Norwegian men and women with standardized weight and height measurements.[24] In that study the relation between body mass index and renal cell cancer was more pronounced in those who never smoked.

The increasing prevalence of obesity may partly explain the increasing incidence of renal cell cancer. In fact, the proportion of renal cell cancers attributable to overweight and obesity is estimated to be more than 40% in the United States and more than 30% in Europe.[23,25]

Obesity and hypertension are believed to act independently as renal cell cancer risk factors in men and women. Lipid peroxidation, which is increased in obese and hypertensive subjects, is hypothesized to be partly responsible for these associations through the formation of DNA adducts.[26] Obesity may act by promoting hormonal changes, such as increased peptide levels, and steroid hormones or increased insulin-like growth factor I associated with increasing body mass index in men and women could contribute to renal cell cancer.[25] Obesity may also predispose to a higher glomerular filtration rate and renal plasma flow independent of hypertension as well as to arterionephrosclerosis, which may in turn render the kidney more susceptible to carcinogenesis.

Hypertension and Antihypertensive Drugs

It is difficult to separate the influences on renal cell cancer risk of hypertension and its treatment with antihypertensive medications. Moreover, early stage, prediagnostic renal

tumors may themselves lead to increased blood pressure. A recent study showed an increasing prevalence of hypertension in the United States, particularly in black individuals and in women,[27] which may explain in part the recent trends of increasing renal cell cancer incidence.

The weight of the epidemiological evidence suggests that it is hypertension, rather than diuretics or other antihypertensive drugs, that influences the development of renal cell cancer. Most but not all studies have demonstrated an increased risk of renal cell cancer even after excluding the first 5 or 10 years before diagnosis, when preclinical disease or undetected renal cell cancers may cause increased blood pressure, rather than the reverse.[9]

The mechanism by which high blood pressure may affect renal cell cancer risk is unclear. However, hypertension induced renal injury may have a role or hypertension may be associated with metabolic or functional changes in the renal tubules that increase susceptibility to carcinogens. The hypothesis that renal cell cancer is more likely to be diagnosed incidentally in patients being treated for hypertension was not supported by a recent analysis.[28]

Animal studies have linked the commonly used diuretics hydrochlorothiazide and furosemide with kidney tumors in rats.[9] Moreover, these compounds act on the renal tubules, which are the site of origin of renal cell cancers. Most recent epidemiological studies suggest that diuretic use is not an independent risk factor for renal cell cancer since adjustment for high blood pressure appears to eliminate any excess risk associated with diuretic use.[11,29] No particular class of other antihypertensive medications has been consistently associated with renal cell cancer risk.[30]

Analgesics

Historically an association between chronic heavy use and abuse of phenacetin containing analgesics and transitional cell cancers of the renal pelvis has been clearly established but their effect on adenocarcinomas of the renal parenchyma is less conclusive.[9] Any association with renal cell cancer is now difficult to assess because phenacetin containing analgesics have been off the market for at least 25 years in most countries and reliable recall of past intake is no longer practical.

With respect to other types of analgesics, most studies have focused on acetaminophen, which is the major metabolite of phenacetin, although several have also presented data on aspirin use. Neither acetaminophen, aspirin nor other types of nonsteroidal anti-inflammatory drugs have been convincingly linked with renal cell cancer. The large, international population based, case-control study showed no link with acetaminophen or aspirin use.[12] Moreover, no consistently increasing risks were observed with increasing consumption. The results of a large study in the United States designed to evaluate this association failed to show any link with regular use or duration of use of acetaminophen.[31]

Diet

Except for the relatively consistent protective effect of fruit and vegetable consumption,[32] convincing evidence linking specific dietary factors and renal cell cancer risk has not been reported. Some epidemiological studies suggest that increased protein consumption may be a risk factor for renal cell cancer but the largest epidemiological study to date failed to provide clear support for this hypothesis.[17] Failure to adjust for confounding by energy intake, and the high collinearity among total calories, protein calories and fat calories make it difficult to disentangle the effects of calorie sources. For the most part it appears that dietary components are unlikely to have a significant role in renal cell cancer etiology.

Alcohol Consumption

Early ecological findings of a relation between kidney cancer and per capita alcohol consumption have generally not been confirmed by case-control and cohort studies of renal cell cancer after adjustment for confounding by cigarette smoking.[9] Moreover, cohort studies of alcoholics and brewery workers have shown no excess mortality due to kidney cancer.[33]

Hormonal and Reproductive Factors

There is little epidemiological evidence linking hormone associated variables to renal cell cancer in humans. In the large, international case-control study a significantly decreased risk was associated with the use of oral contraceptives but it was restricted to women who did not smoke,[15] while another study showed no such relationship.[34] Similarly the association between prior hysterectomy or oophorectomy and the risk of renal cell cancer has been inconsistently reported.[15,34]

Occupation

Renal cell cancer is not generally considered an occupationally associated tumor.[9] However, numerous epidemiological studies have been performed during the last 3 decades that included queries on occupation and a number of sporadic associations have been reported between exposure or jobs/industries and renal cell cancer. Asbestos was linked to kidney cancer in 2 cohort studies, including 1 of insulators and 1 of asbestos product workers.[9] A positive association between self-reported asbestos exposure and renal cell cancer was reported in several other case-control studies, including a large international study that included 200 exposed cases and showed a moderate relative risk of 1.4 with self-reported asbestos exposure.[14] However, data on the duration of exposure did not support an association. An extensive meta-analysis of occupationally exposed cohorts indicated little association between kidney cancer risk and asbestos exposure.[35]

In the early 1980s gasoline was suspected as a risk factor for renal cell cancer when male rats exposed in the long term to unleaded gasoline vapors developed a significant excess of renal cancers. Since then, a number of epidemiological studies have examined the effect of gasoline exposure and the collective evidence to date does not support a relationship between gasoline and the risk of renal cell cancer.[36] No association with gasoline was observed in numerous occupational cohort and nested case-control studies performed in different exposed worker populations,[37,38] and a recent mortality and cancer morbidity study in a cohort of Canadian petroleum workers did not indicate an excess of kidney cancers.[39] Finally, the bioassay finding in male rats was due to a unique sex and species related compound α2-microglobulin, which is unlikely to be relevant to humans.[36]

Considerable interest has recently focused on the solvent TCE, largely as a result of animal findings and of 3 studies performed in the same area of Germany.[40] These studies were initiated in response to a cluster of renal cell cancer cases reported at a cardboard manufacturing plant. All 3 studies showed a strikingly increased relative risk of renal cell cancer associated with TCE exposure.[40] These findings contrast starkly with the results of other investigations and several serious methodological shortcomings of these studies have been noted,[41–43] limiting any conclusion that can be drawn. To date 7 cohort studies have evaluated the relationship between TCE and specific types of cancer. The 2 largest studies to date of the association between TCE exposure and cancer used sophisticated methods of exposure assessment, and internal and external comparisons.[44,45] Neither of these studies showed a significantly increased risk of renal cell cancer in TCE exposed workers. The most recent cohort study, which was performed in Denmark, evaluated cancer morbidity in 40,049 workers with presumed exposure to TCE.[46] It demonstrated a weak association between renal cell cancer and TCE at high levels of exposure in the distant past. However, the weight of the evidence to date does not provide consistent, credible support for the hypothesis that TCE is a cause of renal cell cancer in humans.

Kidney Transplantation and Dialysis

Patients undergoing long-term renal dialysis experience a substantially higher average annual incidence of renal cell carcinoma than the general population[47] and the risk appears to increase with increasing duration of dialysis. Acquired renal cystic disease of the native kidneys is believed to be the major risk factor for renal cell carcinoma in patients on dialysis independent of patient age or underlying renal disease.[48] Several recent studies of cancer risk subsequent to kidney transplantation showed a substantially increased risk of acquired renal cystic disease and renal cell cancer compared with that in the general population.[49]

Radiation

Ionizing radiation appears to weakly increase the risk of renal cell cancer in patients treated for ankylosing spondylitis and cervical cancer. An increased risk was also observed in patients receiving radium 224 for bone tuberculosis and ankylosing spondylitis.[9]

CONCLUSIONS

A further reduction in cigarette smoking and a decrease in the rates of obesity and probably hypertension would likely curb to some degree the increasing incidence of renal cell cancer. Focused analytic epidemiological studies, including the evaluation of gene-environment interactions, are needed to specifically identify reasons for the increasing incidence in the last 25 years since a large proportion of renal cell cancers are not accounted for by risk factors, including cigarette smoking, obesity and hypertension. Particular attention should be focused on black Americans because their incidence rate has increased in the last 3 decades to significantly surpass that of white Americans. The roles of hypertension, obesity and genetics in this and other high risk populations should be thoroughly evaluated.

Abbreviations and Acronyms

SEER = Surveillance, Epidemiology, and End Results
TCE = trichloroethylene

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