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Epidemiology and risk factors for kidney cancer

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Abstract

After over two decades of increasing rates, kidney cancer incidence trends worldwide show signs of plateauing or decreases in recent years. In the United States, rates for renal cell cancer, the predominant form of kidney cancer in adults, continue to rise but mainly for early stage tumors. Incidence rates for renal pelvis cancer have declined, while kidney cancer mortality rates overall have leveled. These patterns are consistent with reports of incidental diagnosis and downward shift of tumor stage and size in clinical series. The changing prevalence of known risk factors for renal cell cancer, including cigarette smoking, obesity, and hypertension, may also be influencing the incidence trends, although their relative impact may differ in various populations,. Evidence is accumulating to suggest an etiologic role for physical activity, alcohol consumption, occupational exposure to trichloroethylene, and high parity among women, but causal conclusions are not yet supported. Genetic susceptibility and its interaction with environmental exposures are believed to influence renal cell cancer risk, but limited studies based on candidate gene approaches have not produced conclusive results. Large consortium efforts employing genome-wide scanning technology are underway, which hold promise for novel discoveries in renal carcinogenesis.

INTRODUCTION

Kidney cancer among adults consists of malignant tumors arising from the renal parenchyma and renal pelvis. Nearly all renal pelvis cancers are of the transitional cell type, comprising less than 10% of the microscopically confirmed kidney carcinomas (Box 1). Adenocarcinomas arise primarily in the renal parenchyma (hence forth referred to as renal cell cancer), accounting for over 90% of kidney carcinomas. The majority of kidney cancer among children is nephroblastoma (Wilms tumor), comprising about 1.1% of all kidney cancers. This malignancy is not a focus of the current review.

By far the majority of renal cell carcinomas with subtype further specified are of the clear cell type, followed by the papillary and chromophobe tumors (Box 1). Although histologic subtypes of renal cell cancer have been shown to differ in clinical features and genetic determinants,[1,2] epidemiologic data on renal cell cancer subtype are sparse and have not revealed consistent patterns.

DESCRIPTIVE EPIDEMIOLOGY

Incidence Patterns

Renal cell cancer incidence rates vary substantially worldwide (Table 1).[3] Rates are generally high in Europe and North America and low in Asia and South America. Within a

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continent, rates also differ by country. Across Europe, incidence among males ranged more than five-fold: from 2.9 per 100,000 in Serbia to 15.2 per 100,000 in the Czech Republic. Even within a country, rates can be dissimilar across regions, such as 3.6 per 100,000 in Salerno and 9.0 per 100,000 in the North East region of Italy. Rates among females are generally about half those among males and also vary geographically.

In the United States, renal cell cancer incidence rates differ among various racial/ethnic populations (Table 1).[3] Rates are lowest among Asian/Pacific Islanders, mirroring rates of their countries of origin. However, incidence rates for white Hispanics are much higher than rates reported in Latin America, suggesting the potential role of environmental exposures.

Compared to renal cell cancer, incidence rates for renal pelvis cancer are much lower (Table 1). Of interest are the diverse male-to-female rate ratios for renal pelvis cancer, with a ratio of two or lower for the majority of countries. This is in contrast to the nearly four-to-one male-to-female rate ratio for bladder cancer,[4] a tumor that is also mostly of transitional cell type and thought to share common risk factors with renal pelvis cancer.

The relatively low incidence rates of renal pelvis cancers reported in Croatia and rates comparable to other European regions reported in Serbia are notable. These countries are located in a region where the Balkan nephropathy, a chronic interstitial kidney disease known to increase the risk of renal pelvis and ureter cancers, is endemic.[5] Despite its endemic nature, Balkan nephropathy appears to have a relatively small impact on the overall occurrence of renal pelvis cancer in this region.

Temporal Trends

Rising kidney cancer incidence has been reported in most countries over the past three decades, but data are limited for the evaluation of renal cell and renal pelvis cancer trends separately.[6,7] Total kidney cancer incidence rates generally rose at least until the mid-1990s when rates leveled or dropped in a number of registries in Europe, Oceania, Asia, and Canada (Figure 1).[3,8] In a few countries, such as Sweden, Hong Kong, and among men in Canada, the decline started earlier. This observation was consistent with patterns seen in some countries in the European Union.[7] In the United States, incidence rates for total kidney cancer (Figure 1) and specifically for renal cell cancer (renal parenchyma) (Figure 2) rose consistently over time, with the increases more rapid among blacks than whites and a shift from a predominance among whites to blacks. Rates for renal pelvis cancer have leveled or even declined.[9] It has been shown that renal cell cancers are being diagnosed at an earlier stage, and among Stage I (localized) tumors, there is a shift towards smaller tumor sizes.[10] Incidental diagnosis of some small tumors have been documented, and are attributed to the more liberal use of imaging procedures.[11] The temporal renal cell cancer incidence trends by stage at diagnosis in the United States support this observation, with most of the increases occurring in tumors at localized stage of disease at diagnosis (Figure 3).[9] When tumor size was examined, the rate of increase in incidence for tumors <2.0 cm by far outpaced tumors of larger sizes, followed by tumors 2.0-4.0 cm in size.[12] However, more modest increases in incidence rates were also observed for tumors of larger sizes, while rates for tumors of unknown size declined. The diagnoses of renal cell cancer at an increasingly early stage and smaller size could have contributed in part to the recent leveling of kidney cancer mortality rates in the United States (Figure 2)[13] and many countries in Europe,[7] although the survival of patients diagnosed with tumors of all stages has also improved over time.[12]

RISK FACTORS

Except for cigarette smoking[14] and the use of phenacetin-containing analgesics,[15] few risk factors are established for renal pelvis cancer.[6] Since the late 1960s, phenacetin became

generally unavailable in most industrialized countries and was eventually banned from the markets. The remainder of this review thus focuses on risk factors for renal cell cancer (Table 2).

Cigarette Smoking

Cigarette smoking is considered a causal risk factor for renal cell cancer by the International Agency for Research on Cancer (IARC) and the U.S. Surgeon General,[16,17] although the risk associated with cigarette smoking is relatively modest. Compared to never smokers, risk increased about 50% in male and 20% in female smokers.[18] A clear dose-response pattern of risk was observed with increasing amount of cigarettes smoked. Smoking cessation reduces the risk, but only among long-term quitters of ten or more years.[12,18] The prevalence of cigarette smoking in industrialized countries generally has declined over time, while it has remained stable or increased in developing countries.[19] These patterns suggest that the relative impact of smoking on future kidney cancer incidence trends may rise in developing countries, while declining in industrialized regions, such as the United States and Western Europe.

Cigarette smoking is hypothesized to increase renal cell cancer risk through chronic tissue hypoxia due to carbon monoxide exposure and smoking-related conditions such as chronic obstructive pulmonary disease.[20] In addition, renal cell cancer patients were shown to have a higher level of DNA damage in their peripheral blood lymphocytes induced by a tobacco-specific N-nitrosamine compared to control subjects.[21] Deletions in chromosome 3p, a frequent site of genetic alterations in renal cell cancer, were also shown to be more common in cultured peripheral blood lymphocyte cells from renal cell cancer patients than control subjects after being treated with benzo[α]pyrene diol epoxide, a major constituent of cigarette smoke.[22]

Obesity

Excess body weight has been estimated to account for over 40% of renal cell cancers in the United States and over 30% in Europe.[23] In prospective studies conducted worldwide, overweight and obese individuals at baseline were found to have elevated subsequent risks of renal cell cancer in a dose-response manner,[24-27] estimated to increase 24% for men and 34% for women for every 5 kg/m^2 increase in body mass index (BMI).[28] Waist-to-hip ratios, weight cycling, and weight gain during adulthood also have been implicated, but their impacts are difficult to disentangle from effects of BMI *per se*.[12] The prevalence of obesity has increased markedly not only in high-resource countries such as the United States and Western Europe, but also in low- and middle income countries since the 1980s.[29] The global rise in obesity likely has contributed to the upward RCC incidence trends, but does not explain the recent leveling of RCC in some countries. Several mechanisms have been hypothesized to influence renal cell cancer development in obese individuals, but direct evidence in humans is limited. These include chronic tissue hypoxia, insulin resistance and a compensatory hyperinsulinemia, altered endocrine milieu and production of adipokines, obesity-induced inflammatory response, and lipid peroxidation and oxidative stress.[30]

Hypertension

Certain types of renal tumors and cancer treatment have been shown to cause hypertension.[31,32] However, there is sufficient evidence to demonstrate that hypertension predisposes to renal cell cancer development. Most studies reported an association with a history of long-term hypertension, and cohort studies with blood pressure measurements taken at baseline generally reported a dose-response of increasing risks with rising levels of blood pressure.[33-36] Users of diuretics and other anti-hypertensive medications also were associated with an elevated risk of renal cell cancer, but an independent effect from that of hypertension *per se*

has not been established.[36-40] In a Swedish cohort study with sequential blood pressure measurements, renal cell cancer risk increased with further elevation of blood pressure and decreased with reduction in blood pressure over time,[33] suggesting a tumor-promoting effect for hypertension and that effective control of blood pressure may reduce renal cell cancer risk. Hypertension is a major chronic disease, estimated to affect about 20% to 40% of the world's population and with increasing prevalence.[41,42] Nevertheless, it is difficult to estimate the extent to which the rising prevalence of hypertension might have contributed to the increasing RCC rates in different populations, as they would also be influenced by the awareness and effectiveness of hypertension control, as well as other contributing risk or protective factors.

Despite the high correlation between obesity and hypertension, their associations with renal cell cancer risk have been shown to be independent of each other. Risk is higher among individuals who are both obese and hypertensive than those who have only one of these conditions.[33,36,39] The biologic mechanisms underlying the association between hypertension and renal cell cancer are unclear, but are hypothesized to include chronic renal hypoxia and lipid peroxidation with formation of reactive oxygen species.[20,43]

Other Prexisting Conditions

A history of diabetes mellitus has been linked to renal cell cancer risk in several cohort studies, but its role independent of those of obesity and hypertension has not been demonstrated conclusively.[34,37,39,44] Elevated risk was statistically insignificant in some studies and tended to diminish to near unity after adjustment for hypertension and body mass index; in other studies, the effects of hypertension and obesity were inadequately adjusted for. Patients with end-stage renal disease were reported to have increased risk of renal cell cancer while undergoing long-term hemodialysis as well as after renal transplantation.[45,46] Further, kidney transplant patients are more likely to have a subsequent renal cell cancer diagnosed in the native kidney than the transplanted kidney.[47] An increased risk of renal cell cancer also has been suggested in patients with acquired renal cystic disease.[48] An elevated risk of a second primary renal cell cancer has been reported among cancer survivors,[49] and the risk of metachronous bilateral renal cell cancer increased monotonically with younger age at diagnosis.[50] Heightened clinical surveillance among patients with these conditions might have contributed to the more frequent diagnosis of a subsequent renal cell cancer.

Reproductive and Hormonal Factors

An increased risk of renal cell cancer has been associated with parity among women in several cohort studies,[51-54] although not all studies supported this observation.[55] Compared to nulliparous women, risk increased 40% to 90% among women who had given birth[51,52,54] and rose with increasing number of births.[51-54] An inverse association with age at first birth has also been reported, with highest risk among women who gave multiple births at a relatively young age.[54] Associations with other reproductive-related factors, including the use of oral contraceptives and hormone replacement therapy, are not consistently observed.[12] Mechanisms underlying the observed association with parity are unclear, although pregnancy-induced hypertension and renal stress may play a role.

Physical Activity

Data linking physical activity to renal cell cancer risk are still limited, but most studies that examined this issue reported an inverse association.[34,39,56-58] A few cohort studies reported a dose-response pattern of further reduction in risk with increasing levels of activity, as assessed by current exercise, routine physical activity, recreational activity, or energy expenditure in a typical day.[39,57,58] Physical activity has been shown to reduce body weight

and blood pressure, improve insulin sensitivity, and reduce chronic inflammation and oxidative stress,[59-61] changes that could contribute to reducing renal cell cancer risk.

Diet and Beverages

Diets rich in fruits and vegetables are inversely related to renal cell cancer risk in a pooled analysis of cohort studies,[62] but the associations with antioxidant nutrients common in fruits and vegetables, such as vitamins A, C, and E, and carotenoids, are mixed.[63-66] Although high consumption of fat and protein, particularly those of animal origin, was suggested as a potential risk factor, a recent pooled analysis of cohort studies and results from a large multicenter European cohort study revealed no association with these macronutrients in multivariate models.[67-69] The role of processed meat, however, may warrant further investigation since a weak association with borderline significance was observed among those with the highest intake, even after adjusting for known renal cell cancer risk factors.[67,69] Self-reported dietary caloric consumption was not related to renal cell cancer risk.[68,70] After removing potential systematic bias using biomarker-calibration, a positive association was observed with energy intake, which was explained in part by BMI.[70]

Acrylamide, a substance classified by the IARC as Group 2A “probable” human carcinogen based on experimental data,[71] was recently detected in unexpectedly high levels in commonly consumed fried and baked foods.[72] Epidemiologic studies assessing the link between acrylamide and renal cell cancer risk, however, have yielded mixed results.[73] Given the ubiquity of acrylamide in foods, continuing monitoring of its carcinogenic potential in humans might be prudent.

Alcohol consumption has been inversely associated with renal cell cancer risk in a dose-response manner in prospective studies, with an estimated 28% reduction in risk among those who drank ≥15 gram/day, equivalent to slightly more than one alcoholic drink per day.[74] The inverse association was observed for all types of alcoholic drinks, including beer, wine, and liquor. In contrast, no association was found with total fluid intake from all beverages or individual type of beverage, including coffee, tea, milk, juice, soda, and water.[75]

Occupation and Environment

Renal cell cancer generally is not considered an occupational disease, but elevated risk has been linked to certain occupations and exposure to a number of industrial agents. Trichloroethylene (TCE), considered a Group 2A “probable” human carcinogen by IARC,[76] is by far the most extensively examined chemical in relation to renal cell cancer risk. Widely used as a metal degreaser and chemical additive, TCE also has become a common environmental contaminant.[77] Epidemiologic evidence linking TCE to renal cell cancer risk is accumulating, with most recent studies reporting rising risk with increasing levels of exposure.[78] The association has been reported in studies employing a variety of study designs and exposure-assessment methods, and being conducted in different populations under various settings. The robustness of the finding across diverse studies raises the likelihood of a true association. However, the difficulties in determining the mode of action and the complexities of TCE pharmacokinetics, co-exposure to other solvents, and various study limitations preclude establishment of a causal conclusion to date.[77-79]

Exposure to other industrial agents, including cadmium and uranium, has not been consistently linked to renal cell cancer risk.[12,80,81] Environmental exposures, such as arsenic, nitrate, and radon in drinking water, also have not been established as risk factors.[12]

GENETIC SUSCEPTIBILITY AND ENVIRONMENT

Inherited renal cell cancer is known to occur in a number of familial cancer syndromes, most notably the von Hippel-Lindau (VHL) syndrome. This syndrome is characterized by alterations in the *VHL* gene and predisposition to a number of diseases among family members, including the clear cell subtype of renal cell cancer.[82] Only a very small proportion of renal cell cancer patients are known to occur in families with these rare syndromes, although the exact percentage is difficult to pinpoint. However, sporadic renal cell cancers have been shown to have a familial predisposition, with a recent meta-analysis showing a greater than twofold risk among individuals having a first-degree relative diagnosed with kidney cancer.[83] The interplay of exposures to environmental risk factors and genetic susceptibility of exposed individuals is believed to influence the risk of developing sporadic renal cell cancer.

Renal cell cancer patients were found to have shorter telomere length in blood DNA compared to control subjects, and the association appeared to be modified by cigarette smoking.[84] Low mitochondrial DNA (mtDNA) content in peripheral blood lymphocytes also was associated with elevated risks of renal cell cancer in a dose-response manner.[85] Although mtDNA content was significantly lower among smokers than non-smokers, smoking did not modify the association between mtDNA and renal cell cancer risk. The findings with telomere length and mtDNA have yet to be confirmed, preferably in larger studies with prospectively collected genomic DNA samples. Studies of signature tumor DNA alterations may also provide clues to relevant environmental carcinogen exposures.[86] Although an earlier link of *VHL* mutations in renal cell cancer to heavy TCE exposure[87] has yet to be replicated in other occupational studies,[88] recent advancement in tumor analysis likely will enhance the opportunities for such discoveries.[89,90]

Renal cell cancer risk has been evaluated in relation to a number of common genetic variants in blood DNA (Table 3). Most of the studies to date were based on candidate gene approach, identifying a few genes in a pathway that may be relevant for renal carcinogenesis and a few single nucleotide polymorphisms (SNP) in the selected genes.[12] The results for most of the genes and SNPs have yet to be replicated in future investigations (Table 3, under Limited Evidence).

Genes encoding the glutathione S-transferase (GST) enzymes, including *GSTM1*, *GSTT1*, and *GSTP1*, are by far the most studied in relation to renal cell cancer risk (Table 3). The GST enzymes are active in the detoxification of polycyclic aromatic hydrocarbons in tobacco smoke, halogenated solvents, and other xenobiotics. Although the *GST* genes generally have not been linked to renal cell cancer risk, associations with tobacco smoke, exposure to TCE or pesticides, and consumption of cruciferous vegetables have been shown to vary among subgroups defined by genotype status. However, inconsistency in subgroup findings among studies, small numbers of exposed individuals, and lack of replication data for some findings suggest that further investigations are needed to clarify these associations.[12]

NAT2, a gene encoding the N-acetyltransferase 2 enzyme that is involved in the metabolism of arylamine in tobacco smoke, also has been evaluated in a few studies of renal cell cancer. Smoking-related risk was found to be higher among those carrying the slow than the rapid acetylator genotype,[91] a finding consistent with that observed for bladder cancer[92] but not yet replicated in renal cell cancer.

Vitamin D maintains calcium homeostasis and has been shown to play a role in cell proliferation and progression to a number of cancers.[93] Genes in the vitamin D pathway have been investigated in relation to renal cell cancer risk, but the findings are not consistent

across the few studies.[12] Recently, a relatively large study from Central and Eastern Europe comprehensively examined eight vitamin D pathway genes with complete genomic coverage, and found increased risk associated with variant haplotypes of the vitamin D receptor gene.[94] The same study also comprehensively examined genes related to lipid peroxidation, blood pressure control, and cellular growth, differentiation, and apoptosis.[95-97] Elevated renal cell cancer risk was associated with two SNPs in the regulatory region of the apolipoprotein E gene, which was replicated in a second large study in the United States.[95] Associations also were observed with the apoptosis genes *CASP1/5/4/12* and blood pressure gene *AGT*, but replication is needed to confirm these findings.[96,97]

Recently, high throughput methods for genome-wide scanning of tagging SNPs and copy number alterations have been developed, and large studies with consortium efforts in relation to disease risks have flourished. Such efforts for renal cell cancer also are underway and likely will accelerate the discovery of common genetic variations and how their interactions with environmental exposures may influence renal carcinogenesis.

CONCLUSIONS

Worldwide, kidney cancer incidence rates increased until the mid-1990s when they stabilized or declined in many countries. In the United States, incidence rates of renal cell cancer, the predominant subtype of kidney cancer, rose through the mid-2000s while rates of renal pelvis cancer declined since the 1990s for blacks and earlier for whites. Most of the increases in renal cell cancer since the 1980s occurred in early stage tumors, a pattern consistent with trends demonstrating a downward shift in tumor stage and size observed in numerous clinical series. The rising prevalence of obesity and hypertension, well-established risk factors for renal cell cancer, are likely to have contributed to the upward cancer incidence trends. The impact of cigarette smoking in industrialized countries should continue to decrease with generally declining consumption, but may grow in developing regions where smoking prevalence shows no sign of abating. There is accumulating evidence to suggest that physical activity, alcohol intake, occupational exposure to TCE, and high parity in women may influence renal cell cancer risk. However, the relative contribution of each of these risk factors to the RCC incidence trends in any population could vary according to the prevalence of other risk and protective factors, awareness and effectiveness in the control of predisposing conditions, and surveillance and incidental diagnosis of preclinical tumors. While only a small proportion of renal cell cancer occur within the milieu of familial cancer syndromes, genetic susceptibility and its interplay with environmental exposures also are believed to play an etiologic role in the development of sporadic renal cell cancer. However, studies of common genetic variants in relation to renal cell cancer risk using the candidate gene approach have yielded mixed results to date. The rapid advancement in laboratory technology for genome-wide scanning will allow for more thorough evaluation of common genetic variations. In conjunction with consortium efforts in pooling detailed exposure data and biological samples from well-designed epidemiologic studies, these innovative technologies hold promise for novel discoveries into the genetic determinants and how their interaction with environment may influence renal cell cancer etiology.

KEY POINTS

- Kidney cancer among adults includes malignant tumors arising from the renal parenchyma and renal pelvis. Renal parenchyma cancer is the predominant kidney cancer, mainly of the adenocarcinoma cell type (renal cell cancer). Renal pelvis cancers are mostly of the transitional cell type.

- Renal cell cancer incidence rates are high in Europe and North America and low in Asia and South America. In contrast, there is generally less geographic variation for the rarer renal pelvis cancers.
- Worldwide, kidney cancer incidence rates increased until the mid-1990s when they plateaued or declined for many countries.
- In the United States, renal cell cancer incidence rates increased while renal pelvis cancer rates decreased over time. Much of the increases in renal cell cancer are due to diagnosis of early stage tumors, suggesting that heightened surveillance may play a role.
- Cigarette smoking, obesity and hypertension are well-established risk factors for renal cell cancer. Evidence is also accumulating to implicate physical activity, alcohol consumption, occupational exposure to TCE, and parity in women as risk or protective factors.
- Studies of common genetic variations using the candidate gene approach in relation to renal cell cancer risk have produced inconsistent results. On-going large consortium studies employing advanced genome-wide scanning technology hold promise for novel discovery of etiologic and prognostic factors for renal cell cancer.

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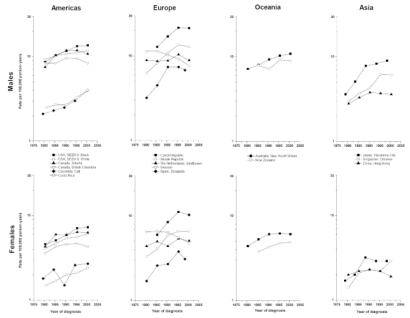

Figure 1.
International kidney cancer incidence rates per 100,000, age-adjusted to the World standard, by gender, continent, and country, 1978-2002.

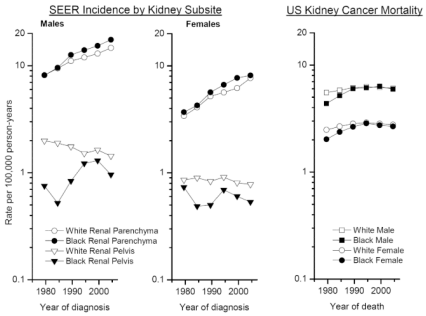

Figure 2.

Kidney cancer SEER-9 incidence rates by subtype and U.S. mortality rates per 100,000, age-adjusted to the U.S. 2000 population, by race and gender, 1977-2006.

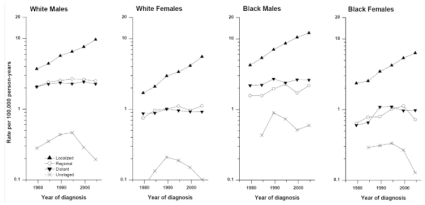

Figure 3.
Renal cell carcinoma SEER-9 incidence rates per 100,000, age-adjusted to the U.S. 2000 population, by race, gender, and stage at diagnosis, 1977-2006.

Table 1

International kidney cancer incidence rates per 100,000, age-standardized to World population, by cancer subtype and gender, Cancer Incidence in Five Continents, Vol. IX, 1998-2002*

	Renal Parenchyma†			Renal Pelvis‡		
	Incidence Rates		M/F Rate Ratio	Incidence Rates		M/F Rate Ratio
Region/Country/Race/Ethnic	**Male**	**Female**		**Male**	**Female**	
North America						
SEER14: Asian/Pacific Islander	4.7	2.2	2.1	0.5	0.2	2.5
Canada, British Columbia	6.5	3.2	2.0	0.6	0.3	2.0
Canada, Alberta	9.1	5.1	1.8	0.6	0.4	1.5
SEER14: White Hispanic	9.7	5.2	1.9	0.6	0.3	2.0
SEER14: White non-Hispanic	10.0	4.8	2.1	0.8	0.4	2.0
SEER14: African American	11.5	5.7	2.0	0.5	0.3	1.7
Asia						
Korea, Incheon	2.8	1.2	2.3	0.7	0.2	3.5
China: Hong Kong	2.9	1.5	1.9	0.3	0.1	3.0
Singapore: Chinese	3.8	1.8	2.1	0.5	0.2	2.5
Japan: Hiroshima§	5.8	1.7	3.4	1.3	0.5	2.6
Europe						
Serbia	2.9	1.5	1.9	0.8	0.6	1.3
Italy, Salerno	3.6	1.6	2.3	0.8	0.2	4.0
Croatia	3.9	1.7	2.3	0.3	0.2	1.5
Spain, Zaragoza	4.7	2.3	2.0	0.7	0.1	7.0
Sweden	6.0	3.6	1.7	0.7	0.4	1.8
The Netherlands, Eindhoven	6.0	3.3	1.8	0.7	0.4	1.8
UK, England, Northern and Yorkshire	6.6	3.4	1.9	0.8	0.4	2.0
Italy, North East	9.0	3.9	2.3	0.7	0.3	2.3
Slovak Republic	9.1	4.4	2.1	0.7	0.5	1.4
Germany, Munich	9.7	4.4	2.2	0.7	0.5	1.4
Czech Republic	15.3	7.2	2.1	1.0	0.6	1.7
Oceania						

	Renal Parenchyma†			Renal Pelvis‡		
	Incidence Rates		M/F Rate Ratio	Incidence Rates		M/F Rate Ratio
Region/Country/Race/Ethnic	**Male**	**Female**		**Male**	**Female**	
New Zealand	6.5	3.4	1.9	0.5	0.3	1.7
Australia, New South Wales	9.0	4.3	2.1	0.8	0.9	0.9
Latin America						
Costa Rica	2.5	1.4	1.8	0.2	0.1	2.0
Brazil, Sao Paulo	4.2	1.9	2.2	0.1	0.1	1.0

*Curado, M.P., et al. (eds.) Cancer Incidence in Five Continents, Vol. IX. IARC Scientific Publications No. 160, Lyon, IARC (2007). Registries were selected if cancer was reportable by legislation or administrative order, >70% of cases with microscopic confirmation, and relatively low percentages of cases treated outside registration area and non-residents treated inside registration area.

†Includes all adenocarcinomas occurring in kidney and renal pelvis, based on IARC classification.

‡Includes transitional cell carcinoma and squamous cell carcinoma occurring in kidney and renal pelvis.

§Year of diagnosis 1996-2000

Table 2

Risk factors for renal cell carcinoma

Risk Factors	Association	Comment
Established*		
Cigarette smoking	Positive	▪ Dose-response with pack-years
		▪ Smoking cessation reduces risk
Excess body weight	Positive	▪ Dose-response with usual adult BMI
		▪ Effect of weight change on risk unclear
Hypertension	Positive	▪ Dose-response with blood pressure
		▪ Control of hypertension may reduce risk
		▪ Effect independent of body weight
Suspected§		
Diabetes mellitus	Positive	▪ Independent effect from obesity and hypertension not yet established
Parity in women	Positive	▪ Dose-response with number of births
Physical activity	Inverse	▪ Dose-response with activity level
Alcohol consumption	Inverse	▪ Dose-response with amount consumed
Trichloroethylene exposure	Positive	▪ Dose-response with exposure level

*Observed in nearly all studies; exposure precedes renal cell cancer; dose-response; risk reduction with removal of exposure

§Observed in numerous studies, but conflicting results in some studies; exposure preceeds renal cell cancer; dose-response; independent effect from known risk factors not established; difficulty in exposure assessment

Table 3

Genetic variants associated with renal cell cancer risk

Pathway	Gene	Main Effect*	No. of studies	Comments
Suggestive Evidence§				
Xenobiotic metabolism	GSTM1	null	7	•significant interaction with pesticide exposure
				▪inconsistent interaction with TCE
	GSTT1	null	6	• significant interaction with pesticides and cruciferous vegetables
	NAT2	null	3	•significant interaction with smoking
Vitamin D Receptor	VDR	increased	3	•comprehensive analysis identified 5 significant SNPs out of 29
				•inconsistent results for RFL polymorphisms
Lipid Peroxidation	APOE/C1	increased	2	•comprehensive analysis identified 3 significant SNPs out of 5
				•comprehensive analysis identified 1 significant region in promoter
				•2 snps (rs405509, rs8106822) replicated in second study population
Limited Evidence§				
--†	8q24			
Blood Pressure Control	AGT			
Cell Cycle Control	CHEK2, CCND1			
Cell growth/apoptosis	EGFR, TGF-β1, CASP1/CASP5/CASP4/CASP12			
Cytokine related	TNF-α, IL4R			
DNA repair	XPD, XPA, XRCC4, ERCC6, NBS1			
Insulin growth factor	IGFBP3			
Matrix metalloproteinase	MMP-1			
miRNA processing	GEMIN4			
One-carbon (folate) metabolism	MTHFR, TYMS			
Oxidative stress/inflammation	COMT, GPX4, NOS2A			
p53 regulation	MDM2			
T-cell regulation	CTLA4			
Vitamin D	RXRA			
Wnt signaling genes	DKK2, DKK3, SFRP4, SMAD7			
Xenobiotic Metabolism	CYP1A1, CYP1B1, GSTP1			

*Refers to published associations either comparing the homozygous variant group or the combination of the heterozygous+homozygous variant to the reference group

[§] Suggestive evidence refers to at least 2 studies evaluating and demonstrating an association for a variant in that gene; Limited evidence refers to one study demonstrating an association out of one or more studies

[†] The biological mechanism underlying the 8q24 region's association with cancer risk has not yet been identified at the time of this review.