

## EPIDEMIOLOGY OF RENAL CELL CARCINOMA

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### INTRODUCTION

Kidney cancer accounts for nearly 2 % of all malignancies globally. It occurs with 189 000 new cases and 91000 deaths from the disease annually (1). More than 80 % of kidney cancers are renal cell carcinomas (RCC), the remainder mainly renal pelvis cancers. Mortality to incidence ratio of RCC is higher compared to other urological malignancies. The increasing incidence seen in most parts of the world cannot fully be explained by increasing availability to medical service and use of imaging procedures but also to increases in the prevalence of etiologic risk factors.

### DESCRIPTIVE EPIDEMIOLOGY

#### INCIDENCE

As a whole, it is difficult to obtain clear descriptive patterns of incidence and mortality from RCC, since population data from different regions are presented merged with pelvis cancer.

The incidence globally of kidney cancer varies considerably among different populations and regions (Fig. 1). The rates are highest in Western and Eastern Europe, North America, Australia and Scandinavia, intermediate in Southern Europe and Japan, and low elsewhere in Asia, Africa and the Pacific (1). Within Europe, there is also a considerably variation in incidence rates (Table 1).

In the United States, incidence rates are somewhat higher among the black than among the white population (2, 3). The estimated numbers of new kidney cancers (ICD-9 189) in 2000 were about 36,000 in North America and 46,000 in the European Union, and in the Scandinavian countries about 3,000 (1).

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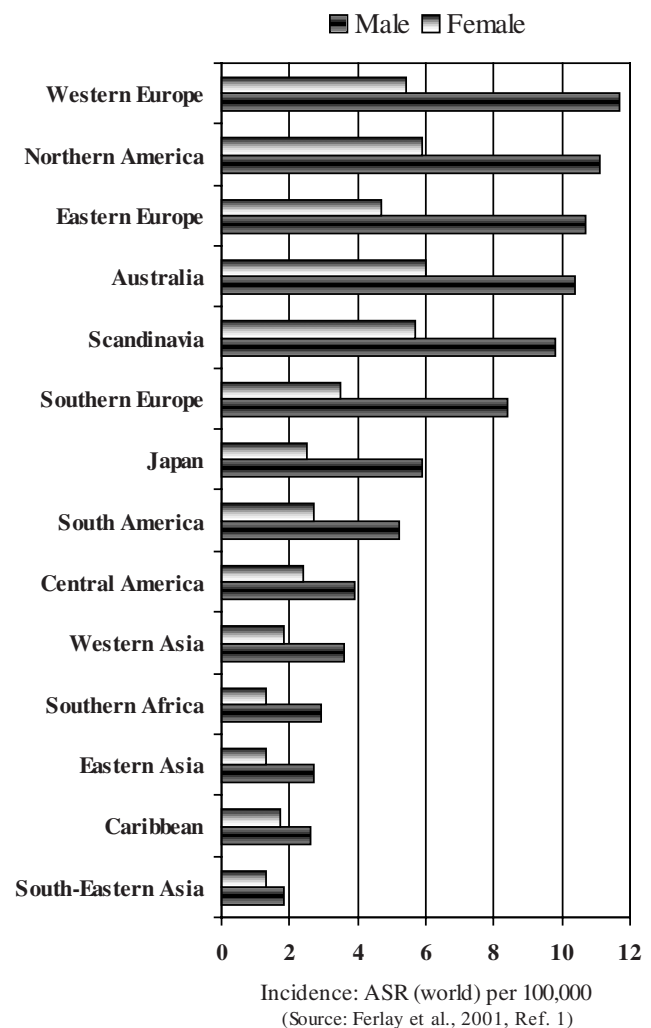


Fig. 1. Kidney cancer incidence.

The geographic variation has been ascribed to differences in diagnostic intensity and autopsy rates as well as to environmental factors that are likely to play an important role in renal cell carcinogenesis. Also, the increasing trend in incidence observed in

TABLE 1  
Range of incidence within Europe in 2000.

Area	Age-standardised rate (world)	
	per 100,000 Men	per 100,000 Women
Scandinavia	8.8–12.5	5.2–7.3
Northern Europe	7.5–16.6	3.8–8.2
Western Europe	7.0–13.0	4.7–5.9
Eastern Europe	6.4–22.2	3.1–10.9
Southern Europe	3.2–10.7	1.1–5.4

(Source: Ferlay et al., 2001).

almost all areas in the world can in part be explained by increased diagnostic surveillance following introduction of new imaging methods such as ultrasonography, computerized tomography (CT) and magnetic resonance imaging (MRI), although declining autopsy rates may have counteracted this trend.

During the last two decades the incidence rates have increased among men and women in all regions and ethnic groups. However, there are a few exceptions notably in Denmark and Sweden, where a decrease in incidence has been observed (4). On the contrary the incidence increased during this period in other Scandinavian countries as Finland and Norway with about 3 % and 1 % per year, respectively. The greatest increase in incidence rates of kidney cancer was observed in some areas in Japan, Italy and Eastern part of Germany, for men with 7 %, 5 % and 5 % per year, respectively. The corresponding increases for women were 4 %, 5 % and 4 %, respectively. For Japan it means an increase of 171 % and 79 % for men and women, respectively, from 1973 to 1992 (4). The reasons for divergent trends in RCC incidence in Scandinavia are unclear. Variations in cigarette smoking patterns may partially explain these observations (4).

Increasing numbers, between 15 % to over 60 % of RCCs are diagnosed incidentally because of the frequent use of ultrasonography, CT and MRI in the investigation of other diseases or conditions. Comparison between reports could be difficult due to varying definitions in classifying an incidentally detected tumour. Most important, tumours found incidentally constitute of a higher proportion of small, low stage tumours, therefore more favourable for cure (5–12). A higher proportion of incidentally detected RCC has been observed in older patients (12).

However, an increase of more advanced tumours has also been reported (2, 8, 13, 14). Most data on renal cell carcinoma stage and presenting symptoms at diagnosis are obtained from large single institutional retrospective series and may therefore represent a selection (14).

The incidence rates are highest in the sixth through seventh decades. Renal cell carcinoma is more common in men than in women; men to women ratios are generally between 1.5:1 and 2.5:1.

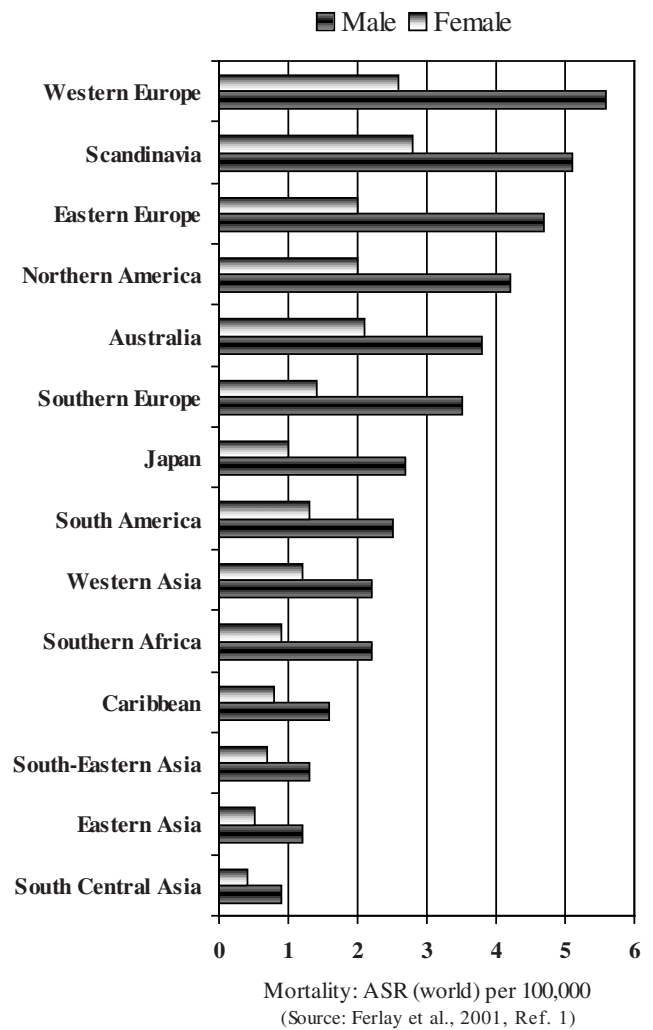


Fig. 2. Kidney cancer mortality.

MORTALITY

Pattern of trends in mortality has followed trends in incidence but with a smaller increase over time due to improvement in survival. The estimated worldwide mortality rates were about 91,000 in year 2000, that is 1.5 % of all cancer deaths (1). Like for incidence there is a considerably variation in mortality among different regions (Fig. 2). The age-adjusted rates for men in Europe varied between about 3 per 100,000 in the southern and 10 per 100,000 in some eastern countries. In North America and Australia mortality rates for men were about 4 per 100,000. In Scandinavia the rates were about 5 and nearly 3 per 100,000 for men and women, respectively. For women in general the rates were about half that of men (Fig. 2) (1).

SURVIVAL

Relative survival of RCC is slightly higher than for transitional cell carcinoma and cancer of the kidney in general. Most population-based survival estimates are based on kidney cancer as one group.

The most important prognostic factor for patients with RCC is still the stage, in spite of other biological and molecular prognostic factors for RCC. Five-year survival rates over all stages are about 40 to over 60 %. In Europe (1990–94) relative survival rates varied from 34 to 68 %. Austria, France, Germany and Italy had a 5-year survival above the European average, while eastern European countries as Estonia, Czech Republic and Poland, and also England, Scotland, and Denmark had survival significantly below the European average. Despite the lack of an effective systemic therapy, a small improvement in overall survival has been noted over the past decades; from an European average 5-year relative survival of 41 %, 48 % to 57 % between 1978–80, 1987–89 and 1990–94, respectively. Women had a slightly higher relative survival than men in the latter period (15, 16). Analyses from several Scandinavian countries have also shown a similar improvement during the last decades (17, 18). Increasing 5-year relative survival rates have also been noted in the United States, from 52 % to 63 % between 1974–76 and 1992–99 (19). This improvement has been achieved primarily owing to early detection and somewhat to advances in the surgical management, rather than of systemic therapies (20).

Patients with localized RCC have a 5-year relative survival between 80 and almost 100 %. The 5-year survival for locally advanced disease, without distant metastasis, varies widely depending on local tumor spread. However, in several large institutional series, stage III disease has a 5-year survival between 60 and 70 %. There is also a significant difference in outcome depending on histologic subtype. The 5-year survival for distant metastatic RCC is less than 10 % (2, 21–28).

The improved survival seen in the 1960s to 70s was likely a result from modification in surgical approach. Improvements seen in the 80s until now most likely reflect the stage migration seen due to the increased use of modern imaging procedures.

## GENETIC AND MOLECULAR EPIDEMIOLOGY

### INHERITED SUSCEPTIBILITY

Although most renal cell carcinomas are sporadic, several genetic diseases are associated with RCC, including von Hippel-Lindau syndrome, hereditary papillary renal carcinoma, tuberous sclerosis, Birth-Hogg-Dubé syndrome and hereditary leiomyoma renal cell carcinoma. The genes underlying each of these conditions have been cloned and germline mutations in affected patients have been identified. Strong correlations have been found between some of these genes involved in the pathogenesis of renal tumours and the histopathological and clinical behavioural features (29–31). For more details on hereditary RCC see chapter "Inherited forms of RCC" by M. Kiuru et al., in this same RCC issue, p. 103.

Few analytical epidemiologic studies have reported on a family history of RCC. One study found a 1.6-fold increased risk for RCC (32) and another a 2.5-

fold risk (33) if a first-degree relative was affected with the disease, whereas no association was found in a smaller study (34). One recent registry study found a 1.6-fold increase for RCC in offspring by parental cancer and a 4.9-fold increase for RCC by sibling's cancer (35).

### ANALYTICAL EPIDEMIOLOGY

#### *Somatic events*

Somatic inactivation of the VHL gene is commonly found in sporadic RCC, which suggests that this is a critical molecular event in renal carcinogenesis. One report identified a "hotspot" for mutations of the VHL gene associated with exposure to trichloroethylene (36). Little information is available on the relationships between VHL gene inactivation and major established environmental risk factors in RCC. Dietary effects on VHL mutations have been addressed, in a small study, with suggestive protective effects of vegetables, citrus fruits and selenium consumption (37). We do not understand the precise role of the gene and we do not know if the inactivation is an important molecular event in the multi-step process of tobacco-induced RCC development.

### RISK FACTORS

#### TOBACCO

Since the 1986 International Agency for Research on Cancer (IARC) Monograph on tobacco, subsequent epidemiologic studies have convincingly demonstrated that there is sufficient evidence that cigarette smoking is a cause of RCC in both men and women. The association is not explained by confounding. A dose-response relationship with the number of cigarettes smoked has been noted in most studies, and a few also noted a reduction in risk after cessation (38).

Both case-control (39–41) and cohort studies (42–45) have linked RCC to tobacco smoking. Relative risks are generally moderate, but the dose-response relationship reported in both men and women is often strong. This observation, together with the decline in risk following cessation supports a causal interpretation of the association between cigarette smoking and RCC (39, 40, 46). Among studies reporting tobacco products other than cigarettes only a few have found an association with smokeless tobacco or positive associations with cigar and pipe smoking (47).

Most of the constituents in cigarette smoke are metabolized or excreted through the urinary tract. It is not clear which of the constituents are responsible for RCC, but nitroso-compounds especially N-nitrosodimethylamine, found in tobacco smoke, have caused renal tumours in several animal species (38). The possible role of nitroso-compounds has gained support from a study where N-nitrosodimethylamine-induced rat clear cell renal tumors were identified with VHL-mutations. This is the first experiment that linked VHL gene mutations to chemical exposure, thereby providing a possible molecular pathway from tobacco smoking to RCC (48, 49). Also,

a gene environment interaction in the development of RCC of smokers has recently been described; individuals with slow acetylator genotype for N-acetyltransferase 2 (NAT2) had a higher risk for RCC than rapid acetylators (50). This suggests that NAT2 is an underlying susceptibility marker for RCC which can exacerbate RCC risk in combination with risk factors as cigarette smoking.

The proportion of RCCs that could be attributed to cigarette smoking is between 21 % and 30 % among men and 9 % and 24 % among women (47) depending on the prevalence of smoking in the population studied.

#### ANTHROPOMETRIC MEASURES

The most consistent finding in epidemiologic studies of RCC is the excess risk among subjects who are overweight or obese, generally measured as body mass index (BMI) (51). About thirty, mostly case-control studies have investigated the relationship and found an association with a few exceptions stronger and more consistent among women; several of them observed a dose-effect trend. The results from prospective cohort studies are in most instances in agreement with the case-control ones (47).

The three biggest published so far – an international multi-center study (52), a study from Los Angeles (53) and a Canadian study (54) showed significant associations between BMI and risk of RCC in both genders, for men stronger in the U.S. study than in the multi-center study. A quantitative review of published studies (55) also showed that increased BMI was equally strongly associated with increased risk of RCC among men and women, in spite of the fact that weight was measured at different ages in the various studies and of differences in controlling for confounding factors.

The mechanisms by which obesity influences renal carcinogenesis are not clear, but there are several plausible biological explanations. For example, sex steroid hormones may affect renal cell proliferation and growth by direct endocrine receptor-mediated effects, by regulation of receptor concentrations or through paracrine growth factors, e.g. epidermal growth factor. Further, obesity is related to a number of endocrine disorders such as decreased levels of sex hormone-binding globulin and progesterone, anovulation, insulin resistance, and increased levels of biologically active insulin-like growth factor (IGF-I). The risk might be mediated via insulin and insulin-like growth factor-I (IGF-I).

Epidemiologic studies indicate that patients with diabetes have increased risk of renal cell cancer (56). If obesity is related to the metabolic syndrome, elevated levels of circulating androgens and growth factors, as well as of unopposed estrogens, may play an important role in the etiology of RCC more generally. Of particular interest is a possible association with androgens, since the age-standardized incidence of RCC in most populations is approximately 50-100 % higher in men than in women. For that reason the findings from a U.S. cohort study (57) with further follow-up of this cohort (58), are of interest, show-

ing an association of increasing waist-to-hip ratio with increasing risk of RCC among women. Further, hypertension which may be an intermediate step in the causal pathway between obesity and RCC could induce renal damage or be associated with metabolic or functional changes within the renal tubules that increase the kidney susceptibility to carcinogenes or promoting agents.

The cumulative evidence from analytical epidemiologic studies is most consistent for obesity to be a risk factor for RCC in both women and men. The attributable risk of obesity was estimated to 13 % in Australia (59), 21 % in the U.S. and Canada (60, 61), and to about 25 % in the European Union (62).

#### PHYSICAL ACTIVITY

A role of physical activity in the development of RCC is plausible, since energy expenditure is an important determinant of adult weight and obesity, but reports are not consistent and the mechanism is unclear.

The impact of physical activity on the risk of RCC has been reported in five case-control (47, 63) and four cohort studies (47, 64). One of the case-control studies found an inverse association with occupational physical activity among men (65) whereas another found an inverse association with recreational activity among both men and women (63). Two of the cohort studies found an inverse association (64, 66). Bergström et al (66), who classified occupations at two subsequent censuses according to physical demands, found a monotonic increase in risk, among men only, with decreasing level of occupational physical activity. In a cohort study of Finnish male smokers, leisure-time physical activity was inversely related to RCC (64).

#### NUTRITION

Results from analytical, mostly case-control studies, suggest that diet may have a role in the development of RCC, although no link between any specific food item or nutrient and risk of RCC has yet been established (51).

Several analytic epidemiologic studies have shown a positive association with meat, milk and margarine, oils or butter. Most case-control studies and some cohort studies have found a protective effect of vegetables and/or fruits, especially strong for dark green and cruciferous vegetables (51, 67-69).

Analyses of specific nutrients and their relation to RCC have linked elevated risks to intake of protein and dietary fat, and decreased risks to carotenes (47). An inverse association has also been documented with other dietary antioxidants (58, 67, 68, 70). Dietary pattern analysis has also suggested a diet characterised by high protein and fat food to be associated with increased risk of RCC (71).

The most consistent finding regarding diet is the protective effect of vegetables/fruit and their nutrient components – although we have few data from human studies on individual antioxidants. Ascorbic acid, alpha-tocopherol, selenium, beta-carotene and

isothiocyanates have all been pointed out as human cancer protectants (72). The protective effect is not likely to be conferred by a single nutrient in a particular food but rather by many substances acting together.

Neither coffee, nor tea drinking has been convincingly associated with RCC, despite numerous studies (51, 68).

#### ALCOHOL

A hypothesized positive association in ecologic studies between alcohol intake and risk of RCC has not been corroborated in analytical studies (47). A few case-control and also cohort studies have found a possible inverse association (51, 58, 69), which seems to be more pronounced in women than in men (51, 73) and possibly is associated with wine consumption (51).

#### REPRODUCTIVE FACTORS AND HORMONES

There is some evidence that certain hormone-related factors are associated with the risk of RCC. Few analytical epidemiologic studies of RCC have focused on reproductive factors or exogenous hormones and those which have, generally found little evidence that factors like parity and hysterectomy/oophorectomy are of importance (47). However, positive associations, even if weak, have been reported occasionally for oral contraceptives and for use of replacement estrogens (47). In contrast, a multicenter case-control study (74) found a significantly reduced risk of RCC following oral contraceptive use among women who did not smoke, with a suggestion of increased reduction with duration of use. Furthermore, some studies have found an increased risk associated with number of births (34, 58, 74–76). The findings from the relatively few investigations dealing with reproductive and hormonal factors remain enigmatic and inconsistent.

#### IONIZING RADIATION

Various types of ionizing radiation have been associated with an excess risk of kidney cancer. Women with cervical cancer, treated with radiotherapy, experienced a small but significantly increased risk (77) as did men treated for testicular cancer (78). Among patients with ankylosing spondylitis who had received X-ray treatment the mortality from kidney cancer was significantly increased (79). Thorotrast, an  $\alpha$ -emitting contrast medium, has been linked to kidney cancer in patients who had undergone retrograde pyelography with thorotrast; however, the cancers are mostly urothelial cancer of the renal pelvis (80, 81). Only one case-control study (82) found a significant positive association among women between any lifetime radiation therapy received and RCC.

#### OCCUPATION

Except for asbestos, no occupational exposure or occupation has been consistently associated with RCC

(83), and even asbestos is unlikely to be responsible for any important increase in RCC risk (84).

Renal cell carcinoma, in contrast to bladder cancer, is generally not considered an occupation-related cancer. However, associations have been reported with exposure or work related to exposure with asbestos in several studies (47), with gasoline and other petroleum products in some (47, 85) but not all studies, and further with hydrocarbons, lead, cadmium, and work or exposure related to drycleaning and laundry (47, 86, 87). Arsenic has been reported to be associated with increased risk for RCC in areas with chronic exposure from drinking water (88, 89).

International Agency for Research on Cancer has considered both trichloroethylene used mainly in metal degreasing and tetrachloroethylene used in drycleaning as carcinogenic in animals, and probably also to humans. However, critical reviews of both cohort and case-control studies concluded that there is no convincing evidence that these solvents pose a risk in humans; findings from cohort studies argue against a causal relationship (90, 91). However, another recent review has a different view, and finds the evidence supporting an association between trichloroethylene and RCC stronger than for any other cancer site. There is also evidence of an association between incidence of RCC among workers exposed to degreasing agents and solvents and to those in both iron and steel and dry cleaning and laundry work industries, although, direct causality cannot be assessed (92, 93). RCC patients with high, cumulative exposure of trichloroethylene have been shown to have more frequent somatic VHL mutations (36), but this finding needs further confirmation.

#### MEDICAL CONDITIONS AND TREATMENT

A number of medical conditions have been associated with RCC, but the evidence is consistent for only few of them. A major concern in the case-control studies is recall bias, especially regarding urinary tract conditions.

#### END-STAGE RENAL DISEASE

Acquired cystic kidney disease, which occurs in end-stage renal disease with progressive development of cysts in a poorly functioning or non-functioning kidney, is strongly associated with the development of RCC. Acquired cystic kidney disease increases in prevalence and severity with increasing years on dialysis. Irrespective of type of dialysis, the proportion increases to 90 % after 10 years of dialysis. A notable sex difference has been observed, men having a higher incidence and more severe cystic change than women (94, 95).

The incidence of RCC in patients with end-stage renal disease has been reported to be up to 40–100-times higher than in the general population (94–98). An increased risk has also been seen in the native kidneys after renal transplantation (99, 100). While proliferation of proximal tubular epithelial cells has been identified as the major pathogenetic mechanism

of cyst formation, hormones (e.g., estrogens) and growth factors and their receptors may stimulate cell proliferation and promote carcinogenesis. This mechanism may also explain, in part, the onset of multiple renal adenomas and bilateral carcinomas which develop in patients with acquired cystic kidney disease (101).

#### UROLOGICAL DISORDERS

Kidney stones have frequently been found to increase the risk of RCC (47), though not in one cohort study (102). Also urinary tract infection has been positively associated with RCC (47). One recent study reported an interaction of urinary tract infection with both sex and cigarette smoking, with the highest risk for male smokers (103).

#### DIABETES MELLITUS

Results from case-control and cohort studies that investigated the role of diabetes mellitus in the etiology of RCC are not consistent. If there is a relationship between diabetes and RCC the mechanisms are unclear, but elevated growth factors and growth factor receptors may be involved (47).

#### HYPERTENSION, ANTIHYPERTENSIVES AND DIURETICS

An increased risk of RCC has been reported following diuretic use in many epidemiologic studies, but the magnitude of the risk has varied substantially, especially for women. Excess risk, to a lesser degree, has also been reported for men (47). The picture is not clear, but in some more recent studies it seems that diuretic use is not an independent risk factor after adjustment for hypertension (53, 104, 105).

Use of non-diuretic antihypertensives has also been investigated in relation to RCC. In a few studies an association has been found. However, a similar dilution of effect for non-diuretic antihypertensive medication after adjustment for hypertension has been reported (47).

Difficulties have arisen in isolating the possible effects of anti-hypertensive medication from the effects of hypertension, which in itself has been linked to RCC (47, 106).

Sometimes RCC may cause hypertension. Many studies have restricted analysis of hypertension to 5–10 years prior to cancer diagnosis and found an association between hypertension and RCC. This makes hypertension unlikely to be a consequence of the cancer. It seems more likely that hypertension is an independent risk factor in the etiology of RCC but the difficulty to separate the effect of hypertension and its medical treatment hampers definite conclusions.

#### ANALGESICS

Phenacetin-containing analgesics have been implicated in the etiology of renal pelvis cancer; their role in the etiology of RCC is less clear. A number of stud-

ies have associated moderately elevated risks with regular or long-term use. However, more recent studies had limited power to evaluate phenacetin because the drug has been unavailable for many years (47).

#### SUMMARY

The increasing incidence of RCC in most populations may in part be due to increasing numbers of incidentally detected cancers with new imaging methods. Further, the increase is not only limited to small local tumours but also includes more advanced tumours, which may to some part explain the still high mortality rates. The variation in incidence between populations may have several other explanations. Traditionally the starting point has included thoughts of environmental exposures, which so far have only in part explained the causes of RCC, by means of cigarette smoking and obesity, which may account for approximately 40 % of cases in high-risk countries (Table 2). Further, the genetic variations may be of importance as a cause of the difference between populations. Continued research in RCC is needed with the knowledge that nearly 50 % of patients die within 5 years after diagnosis. The further search for environmental exposures should take in account the knowledge that RCC consists of different types with specific genetic molecular characteristics. These genetic alterations have in some cases been suggested to be associated with specific exposures. Furthermore, there might exist a modulating effect of genetic polymorphisms among metabolic activation and detoxification enzymes. Hence, a further understanding of the genetic and molecular processes involved in RCC will hopefully give us a better knowledge how to analyse and interpret exposure associations that have importance for both initiation and progression of RCC.

TABLE 2  
*Risk factors for RCC.*

Established	Needing further study or controversial
Cigarette smoking	Dietary factors
Obesity	Vegetables and fruit – protective
Acquired cystic kidney disease	Protein and/or dietary fat
Inherited susceptibility (e.g. VHL)	Hypertension and/or antihypertensive medication
	Analgesics
	Reproductive factors and hormones (e.g. parity, oral contraceptives)
	Occupational exposures (e.g. asbestos, cadmium, hydrocarbons, gasoline, trichloroethylene)

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