
Kidney Cancers

CHAPTER 7

Epidemiology of Renal Cell Carcinoma

Wong-Ho Chow, Susan S. Devesa, and Joseph F. Fraumeni, Jr.

Malignant tumors of the kidney account for more than 2% of cancer incidence and mortality in the United States, with nearly 30,000 new cases and 12,000 deaths estimated for 1998 (1). More than 80% of kidney cancers arise in the renal parenchyma, with the remainder in the renal pelvis (2). Nearly all kidney cancers originating in the renal parenchyma are adenocarcinomas (renal cell carcinoma), whereas the vast majority of renal pelvis cancers are transitional cell carcinomas. It is estimated that 80% to 85% of the renal cell carcinomas are of the clear cell type, while approximately 10% are of the papillary type, with the remainder consisting of rare histologic types, such as oncocytomas and chromophobe carcinomas (3,4).

The etiology of renal carcinomas varies by subsite of origin. Cigarette smoking and phenacetin-containing analgesics (now withdrawn from most markets worldwide) are the major determinants of renal pelvis cancer (5-7), whereas the risk factors for renal cell carcinoma are more diverse. The remainder of this chapter focuses on renal cell carcinoma.

DESCRIPTIVE EPIDEMIOLOGY

Incidence Patterns

Based on data from the U.S. Surveillance, Epidemiology, and End Results (SEER) program (8), the age-adjusted incidence rates of renal cell carcinoma during 1975 to 1995 for white men, white women, black men, and black women were 9.6, 4.4, 11.1, and 4.9 per 100,000 person-years, respectively. Incidence rates increase consistently with age before plateauing at approximately age 70 years (Fig. 7.1).

Overall, rates for men are more than twice those for women, with the excesses most prominent after age 40 years. In both men and women, rates are higher among blacks than whites younger than age 60 years.

Asians in the United States have incidence rates of renal cell cancer at approximately half the rate of those in other major racial and ethnic groups, including whites, blacks, Hispanics, and American Indians (2,7,9). Internationally, incidence rates tend to be low in Asian countries and high in the United States and Canada (Fig. 7.2) (10). Low rates have been reported in Central and South America, although cancer ascertainment and subsite specificity may be incomplete in some registries. The highest rates in the world have been reported in several central European countries, although rates vary substantially across Europe.

Geographic patterns of age-adjusted incidence (8) and mortality rates (11) have not revealed evidence of an urban versus rural gradient, as suggested in some earlier studies (7,12). Studies examining educational level, a crude measure of socioeconomic status, have shown no clear relation to renal cancer (7), nor has a consistent association with income or social class been observed (13-17).

Time Trends

Incidence rates of renal cell carcinoma and mortality rates of kidney cancer have increased steadily over time in the United States (Fig. 7.3) (18). Between 1975 and 1995, incidence increased annually by 2.3% among white men, 3.1% among white women, 3.9% among black men, and 4.3% among black women. Since the mid-1980s, the incidence rates among blacks have exceeded those among whites of

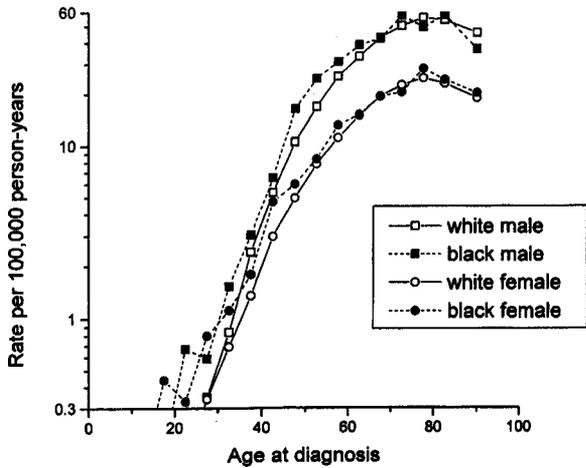


FIG. 7.1. Age-specific incidence rates per 100,000 person-years for renal cell carcinoma by gender and race, U.S. Surveillance, Epidemiology, and End Results, 1975–1995.

both sexes. Rapid increases in the incidence of kidney cancer also have been observed in other countries (10,19–21). To a lesser extent, mortality rates for kidney cancer also have been rising among the four major race and gender groups in the United States (see Fig. 7.3).

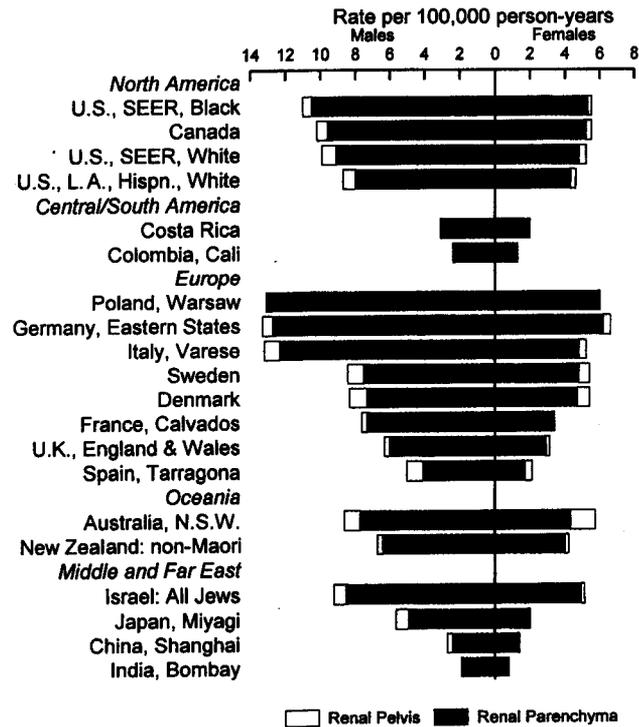


FIG. 7.2. International variation in age-adjusted (world standard) incidence of total kidney cancer, renal cell cancer, and renal pelvis cancer by gender, 1988–1992. (Data from Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J. *Cancer incidence in five continents*, vol VII [IARC Sci. Pub. No. 143]. Lyon, France: International Agency for Research on Cancer, 1997.)

Clinical surveys of patients with renal cell carcinoma have revealed that the incidental detection of renal tumors is rising, owing at least partly to increased use of imaging procedures such as ultrasonography, computed axial tomography scanning, and magnetic resonance imaging (22–24). Examination of incidence rates over time by tumor stage supports this observation, because the most rapid increases are seen for localized tumors (Fig. 7.4). Upward trends also are observed, however, for tumors diagnosed at more advanced stages, except for distant tumors among white men and women. These patterns suggest that the diagnosis of presymptomatic tumors is not likely to fully explain the upward trends of renal cell carcinoma.

Stage at Diagnosis and Survival

Overall, approximately one-half of the renal cell carcinomas reported to the SEER program from 1975 to 1995 were diagnosed while localized, with regional and distant tumors comprising approximately 20% and 25%, respectively (Table 7.1). The distribution by stage at diagnosis is generally comparable among the four race and gender groups, except for a slightly higher proportion of localized tumors accompanied by a slight deficit of regional tumors among blacks compared to whites.

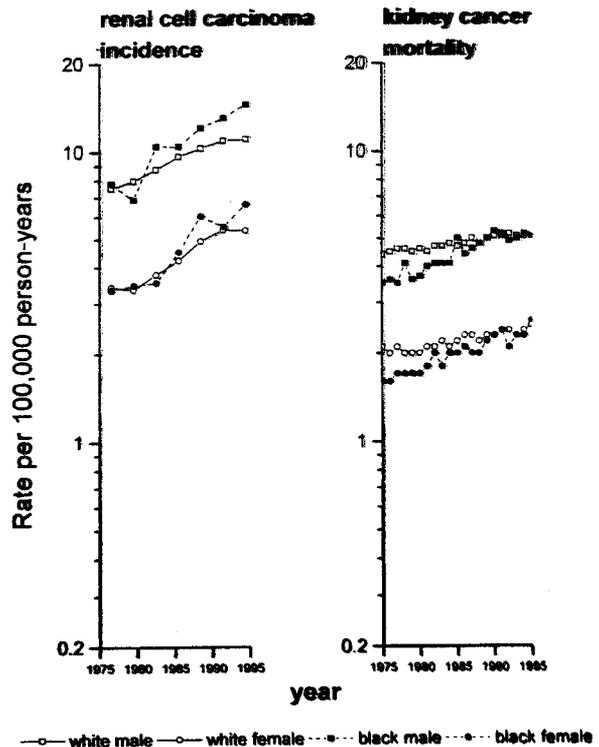


FIG. 7.3. Age-adjusted (1970 U.S. standard) U.S. Surveillance, Epidemiology, and End Results incidence rates for renal cell carcinoma and U.S. mortality rates for total kidney cancer per 100,000 person-years by gender and race, 1975–1995.

TABLE 7.2. Relative 5-year survival rate (%) for renal cell carcinoma by gender, race, and time period, SEER,* 1975–1995

Stage at diagnosis	White male		White female		Black male		Black female	
	1975–1985	1986–1995	1975–1985	1986–1995	1975–1985	1986–1995	1975–1985	1986–1995
Total invasive	50	61	49	59	50	51	55	58
Localized	82	89	82	86	82	75	83	84
Regional	54	62	48	59	52	52	49	44
Distant	7	9	5	7	10	7	6	8
Unstaged	35	31	27	21	24	21	33	35

*Surveillance, Epidemiology, and End Results program supported by the National Cancer Institute.

against early detection of preclinical tumors as the sole explanation for the increasing incidence trends of renal cell carcinoma.

RISK FACTORS

Several risk factors have been implicated in the development of renal cell carcinoma, including environmental exposures, such as smoking and certain medications; preexistent conditions, such as obesity and hypertension; and genetic predisposition. Most of the information on risk factors has come from case-control studies, although cohort studies and family-based investigations have also contributed new insights.

Cigarette Smoking

Although the findings are not entirely consistent, most case-control studies have reported significantly elevated risks of renal cell carcinoma among cigarette smokers (12,14–16,25–36). The absence of significant association in a few studies may be partly explained by small sample size and the use of hospital controls with a high prevalence of smoking (13,37–41). Cohort studies with sufficient sample size have been generally positive, with a follow-up of U.S. veterans showing a clear dose-response relation (42–44).

The relative risks reported with cigarette smoking have been moderately elevated, ranging from 30% to twofold. A dose-response relation has been observed in both men and women, whereas the risk has been shown to decline after smoking cessation (15,31,33,34,36). In one large international case-control study, those who quit smoking for more than 25 years had a risk reduction of 15% compared to current smokers (34), but other studies have reported greater decreases in risk (7,36). An association with other tobacco products, including cigars, pipes, and chewing tobacco, has not been consistently observed (12,16,25–27,33–37).

Population-based attributable risks indicate that between approximately 27% to 37% of the renal cell cancers in men and 10% to 24% in women may be caused by

cigarette smoking (25,30,45). It is unlikely, however, that cigarette smoking has contributed to the upward trends of renal cell cancer, because the prevalence of smoking in the United States has declined since the mid-1960s (46).

Obesity

With a few exceptions (39,47,48), nearly all studies examining the relation of body weight and renal cell carcinoma have found a positive association. Obese persons have experienced elevated risks of 20% to more than threefold, with risks generally greater in women than men. The risks tend to rise with increasing levels of body mass index. The range of risks found in case-control studies (12,14,25,26,29–33,37–40,49–54) are comparable to those reported in several cohort studies (44,55–60), reinforcing the validity of this association. Weight fluctuation (51) and weight gain during adulthood (25,60) have been suggested as independent risk factors, but have not been consistently observed (38,52,53).

In a case-control study conducted in Minnesota, it was estimated that approximately 20% of renal cell cancer cases are attributable to excess weight (45). Thus, the marked increases in the prevalence of obesity in the United States during the past few decades (61) may have contributed to the rising incidence of this cancer. The mechanism by which obesity predisposes to renal cell cancer is unclear. Obesity may influence risk by increasing the levels of endogenous estrogens (62), because estrogenic compounds have been shown to induce renal carcinoma in hamsters (63,64). Obesity also may increase the bioavailability of free insulin-like growth factors (65), which may be involved in renal carcinogenesis (66). In addition, obesity predisposes to hypertension, arterio-nephrosclerosis, and metabolic changes that may render the kidney more susceptible to tumor induction (67,68).

Hypertension

Most epidemiologic studies that have examined the relation between hypertension and risk of renal cell carcinoma have found excess risks ranging from 20% to nearly threefold. It

remains unclear, however, whether hypertension or its treatment is the main risk factor. After adjustment for use of diuretics and other antihypertensive medications, some studies have found that the hypertension-related risk remains elevated (49,69–72), whereas others have found that the risk is attenuated to insignificant levels (26,31,48,73–75). Still others have not adjusted for medications because their use is highly correlated with hypertension (25,29,43,47,54,59,76–78). Although some investigations have found an excess risk only among hypertensive subjects who were medically treated (44,60,79), it is possible that treatment reflects severity of underlying disease and prolongs the course of hypertension and associated renovascular and other changes that may promote the development of cancer.

Because certain types of renal cell carcinoma can cause hypertension (80), several studies have focused on the risks among patients with long-term hypertension. Similar or greater excess risks were reported among hypertensive patients diagnosed from 5 to more than 20 years earlier (29,43,49,54,79), suggesting that the elevated risk of hypertension is unlikely to be an early manifestation of renal tumors.

In the United States, national surveys indicate that the prevalence of hypertension in the population remained relatively stable between 1960 and 1980, but subsequently declined (81). Thus, it would appear unlikely that hypertension has contributed to the rising incidence of renal cell cancer. Because the number of prescriptions and variety of medications used for treatment of hypertension have increased consistently (82,83), however, it is important to separate the effects of hypertension from various antihypertensive medications in the etiology of renal cell carcinoma.

Medications

Diuretics have been linked to renal cell carcinoma in several epidemiologic studies, including follow up of cohorts of patients hospitalized for conditions requiring diuretic treatment (84,85). The elevated risk has varied from 30% to fourfold (26,29,31,44,47–49,54,60,71–75,78,79,86,87), with a dose-response relation suggested in a few studies (48,72,75,79,87). Some studies have reported that the elevated risk is mainly among women (26,29,31,48,74,86,87) and that the risks associated with various classes of diuretics are generally similar (54,72–75,79). In some studies, the excess risk associated with diuretics has been mainly among hypertensive patients (54,78,79), but the findings are not consistent and it has been hard to disentangle the effects of diuretics from hypertension per se or from other antihypertensive drugs.

In studies of renal cell cancer, the risks reported for other antihypertensive medications have varied from unity to increases greater than twofold, but no particular class of drugs has been singled out in the positive studies (28,29,49,54,71–75,78,79,88).

As with diuretics, it has been difficult to distinguish treatment effects from the underlying disease. The problem is complicated by the insidious nature and inconsistent definition of hypertension (89), the potential for misclassification of highly correlated events, and the possible confounding by factors that influence the development and course of hypertension and renal cell cancer, such as obesity (68). Advances in molecular genetics may help to further delineate the effects of hypertension from its treatment by incorporating genetic polymorphisms in drug metabolism in epidemiologic studies of gene-environment interactions in renal cell cancer.

After attempts to adjust for the effect of obesity, the use of diet pills, including those containing amphetamine, has been associated with risk of renal cell cancer, but it has been difficult to truly control for the independent effect of obesity (26,49,50–54).

Analgesics have been related to renal cell cancer in some studies, but the epidemiologic evidence is not conclusive. Major suspicion from case-control and cohort studies has centered on phenacetin-containing analgesics, although the data are less persuasive than for renal pelvis cancer (25,28,29,31,74,90–92). Little support exists in the literature for an association with aspirin products or acetaminophen (7). Because phenacetin products have been generally unavailable in the United States and elsewhere since the 1970s and were withdrawn from the U.S. market in 1983 (93), any impact of phenacetin on renal cell cancer risk should diminish over time. Furthermore, acetaminophen is a major metabolite of phenacetin (94), and its use in the United States did not become widespread until the mid-1970s, so continued monitoring of risks associated with acetaminophen use is needed.

Preexisting Renal Conditions

Increased incidence of renal cell carcinoma has been observed among uremic patients undergoing hemodialysis, particularly among those with acquired cystic kidney disease (95–98). The prevalence of acquired cystic disease has been shown to increase with years on dialysis (95,99), suggesting that this condition represents a precursor state to renal cell cancer.

An elevated risk of renal cell carcinoma has been associated in some studies with a number of kidney diseases, including stones, cysts, and infection (14,17,25,39,49,71,74). The findings, however, have not been consistent (25–28, 31,33,54), suggesting that recall bias and unstable risk estimates caused by small study size may contribute to the reported associations. In a cohort study with long-term follow-up of patients hospitalized for kidney or ureter stones, no excess risk of renal cell cancer was found (100).

The role of developmental defects in renal cell cancer has been suggested by reports of associated renal anomalies, including polycystic kidneys (101), horseshoe kidneys (102), and familial glomerulopathy (103).

Diabetes Mellitus

An elevated incidence of renal cell carcinoma has been observed during long-term follow-up of patients hospitalized for diabetes mellitus (104–106), although mortality from renal cancer was not increased in an earlier cohort of diabetic patients (107). Cohort studies involving the general population, however, have shown little evidence of an association based on small numbers of cases with both conditions (43,60). Several case-control studies have reported a positive association of borderline significance (17,54,71,108), whereas others have found no significant relation (29,31,33,37,49,74,109). Given the strong correlation between diabetes and the risk factors of obesity and hypertension, a detailed assessment of potential confounding by associated conditions is needed before a causal link between diabetes mellitus and renal cell carcinoma can be accepted.

Reproductive and Hormonal Factors

A potential hormonal mechanism for renal cell carcinoma is suggested by animal models showing estrogen-induced renal adenomas and carcinomas in hamsters (63,64,110) and by the finding of sex hormone receptors in normal and malignant renal tissue (111,112). Although obesity is thought to possibly increase risk by promoting hormonal changes, the epidemiologic evidence relating renal cancer to reproductive factors or exogenous hormones is scarce (7). Some studies have suggested an increased risk associated with number of births, particularly among women with a history of hypertension or high body mass index (31,113,114). If this observation is confirmed, it may provide clues to mechanisms of renal dysfunction that predispose to renal cell carcinoma.

Diet and Beverages

Epidemiologic studies of renal cell cancer have linked excess risks with intake of certain meats (13,14,25,29,31,115), dairy products (25,28,116,117), and margarine and oils (39), but associations with specific food items have not been consistently observed. In a large international study, excess risk was related to fried or sautéed and well done or charred meat but not to meat in general (118), suggesting a possible effect of pyrolysis compounds, such as heterocyclic amines, produced during high-temperature cooking of meat (119). Still unclear is whether any specific macronutrient, such as protein or fat, or total caloric intake elevates risk (14,115,118).

Most studies of renal cell carcinoma evaluating the association with fruits and vegetables have found a reduced risk with selected foods (14,29,39,47,116–118), although micronutrients that are common in plant sources, such as vitamin C and carotenoids, have not been consistently implicated (14,60,115–118). Overall, the limited evidence to date suggests that a prudent diet low in animal protein and fat and

high in fruits and vegetables may protect against renal cell cancer.

A relation between renal cell cancer and consumption of alcohol, coffee, and tea has been suggested in some studies, but the overall epidemiologic evidence suggests no clear association with these beverages (7,120,121).

Occupation

Renal cell cancer is generally not considered an occupational cancer, but reports of increased risk among several occupational groups exist, including insulators and shipyard workers exposed to asbestos (122–124), coke-oven workers exposed to polycyclic aromatic hydrocarbons (124,125), dry cleaners exposed to a variety of solvents (124,126,127), oil refinery workers and service station attendants exposed to gasoline and other petroleum products (124,128,129), and workers exposed to lead and cadmium (124,130). In addition, increased risk has been reported among pulp and paper mill workers (131), paperboard printing workers (132), cardboard workers (133), and architects (134). None of these occupations or exposures, however, have been conclusively related to risk in epidemiologic studies. It is noteworthy that a mutational hot spot in the von Hippel–Lindau (*VHL*) gene was found in tumor DNA of renal cell cancer patients with high cumulative exposure to trichloroethylene, but not in tumors of unexposed patients (135). This observation raises the possibility that trichloroethylene may be a renal carcinogen and suggests that further assessment of occupational risk of renal cell cancer is warranted.

Genetic Factors

The role of genetic susceptibility is evident from numerous reports of familial renal cell cancer, studies of which have led to the identification of genes responsible for different syndromes of inherited carcinomas of the kidney (136–139). To date, three major dominantly inherited forms of renal cell cancer have been described (3,4,140). Tumors associated with *VHL* syndrome are predominantly of the clear cell type and are associated with germline mutations of the tumor suppressor *VHL* gene located on chromosome 3p (141). Familial occurrence of clear cell renal cancer also has been described in the absence of *VHL* syndrome and has featured constitutional balanced translocations involving chromosome 3p (142). Hereditary papillary renal cell carcinoma is related to germline mutations of the *MET* protooncogene located on chromosome 7q (137,143). It is noteworthy that somatic mutations in the *VHL* and *MET* genes have been described in a high proportion of sporadic cases with clear cell tumors and in some papillary tumors, respectively, implicating these genes in the development of renal cell cancer generally (143–145). Evidence exists that other genes may contribute to the origins of renal cancer, as suggested, for example, by studies of families with heredi-

tary renal oncocytoma (146). Whether the risk factors identified for renal cell cancer vary by histologic and molecular categories remains to be determined.

Polymorphisms in metabolic genes involved in the activation or detoxification of environmental or endogenous agents have been linked to risk of certain cancers (147-149). Data on renal cell cancer are scarce, however, except for a few small studies exploring the role of *GSTM1*, which encodes an enzyme that is involved in detoxifying polycyclic aromatic hydrocarbons from cigarette smoke and other sources; the role of *GSTT1*, which catalyzes the detoxification of a wide range of endogenous and exogenous compounds, including oxidized lipid and DNA, epoxides, and certain chlorinated solvents; and a study of *NQO1*, which is implicated in detoxification of quinone compounds (150,151). Given the moderate risks associated with cigarette smoking, use of various medications, and other risk factors, the evaluation of polymorphic genes involved in metabolizing tobacco carcinogens and other exposures may help to clarify risk estimates, gene-environment interactions, and mechanisms of renal carcinogenesis.

CONCLUSIONS

Convincing epidemiologic evidence exists linking cigarette smoking, obesity, and hypertension and its treatment to an elevated risk of renal cell carcinoma. In combination, these three factors are estimated to account for nearly 50% of cases in a U.S. population (45) and may have contributed to the increasing incidence trends as well as the racial disparities. Preventive measures aimed at reducing these exposures will help to lower incidence rates. The 50% of unexplained cases, however, underscores the need for further research into the environmental and genetic determinants of this increasingly common cancer. In particular, work is needed to disentangle the effects of hypertension from its treatment and to identify antihypertensive medications that are not related to renal cancer risk. The role of obesity also warrants further clarification, including its mechanisms of action and its determinants, including dietary factors and physical activity that may independently affect the risk of renal cell cancer. Discoveries in the molecular genetics of renal cell carcinoma provide new opportunities to clarify the multifactorial origins of this tumor, including gene-environment interactions that may be unraveled by epidemiologic studies that incorporate biochemical and molecular biomarkers. Finally, the high survival rates for patients diagnosed with localized tumors indicate the importance of early detection and the screening of high-risk individuals to reduce mortality from renal cell cancer.

REFERENCES

- Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics, 1998. *CA Cancer J Clin* 1998;48:6-29.
- Devesa SS, Silverman DT, McLaughlin JK, Brown CC, Connelly RR, Fraumeni JF Jr. Comparison of the descriptive epidemiology of urinary tract cancers. *Cancer Causes Control* 1990;1:133-141.
- Linehan WM, Lerman MI, Zbar B. Identification of the von Hippel-Lindau (VHL) gene. *JAMA* 1995;273:564-570.
- Zbar B, Lerman M. Inherited carcinomas of the kidney. *Adv Cancer Res* 1998;75:163-201.
- McCredie M, Stewart JH, Ford JM. Analgesics and tobacco as risk factors for cancer of the ureter and renal pelvis. *J Urol* 1983;130:28-30.
- McLaughlin JK, Silverman DT, Hsing AW, et al. Cigarette smoking and cancers of the renal pelvis and ureter. *Cancer Res* 1992;52:254-257.
- McLaughlin JK, Blot WJ, Devesa SS, Fraumeni JF Jr. Renal cancer. In: Schottenfeld D and Fraumeni JF Jr, eds. *Cancer epidemiology and prevention*, 2nd ed. New York: Oxford University Press, 1996:1142-1155.
- Ries LAG, Kosary CL, Hankey BF, et al., eds. SEER Cancer Statistics Review, 1973-1995. Bethesda MD: National Cancer Institute, 1998.
- Miller BA, ed. Racial/ethnic patterns of cancer in the United States, 1988-1992 [NIH Pub. No. 96-4104]. Bethesda MD: National Cancer Institute, 1996;56-60.
- Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J. Cancer incidence in five continents, vol VII [IARC Sci. Pub. No. 143]. Lyon, France: International Agency for Research on Cancer, 1997.
- Devesa SS, Grauman DG, Blot WJ, Pennello G, Hoover RN, Fraumeni JF Jr. Atlas of cancer mortality in the United States, 1950-94. Bethesda MD: National Cancer Institute, 1999 (*in press*).
- Wynder EL, Mabuchi K, Whitmore WF Jr. Epidemiology of adenocarcinoma of the kidney. *J Natl Cancer Inst* 1974;53:1619-1634.
- Armstrong B, Garrod A, Doll R. A retrospective study of renal cancer with special reference to coffee and animal protein consumption. *Br J Cancer* 1976;33:127-136.
- Maclure M, Willett W. A case-control study of diet and risk of renal adenocarcinoma. *Epidemiology* 1990;1:430-440.
- La Vecchia C, Negri E, D'Avanzo B, Franceschi S. Smoking and renal cell carcinoma. *Cancer Res* 1990;50:5231-5233.
- Mellemgaard A, Engholm G, McLaughlin JK, Olsen JH. Risk factors for renal cell carcinoma in Denmark. I. Role of socioeconomic status, tobacco use, beverages, and family history. *Cancer Causes Control* 1994;5:105-113.
- Schlehofer B, Pommer W, Mellemgaard A, et al. International renal-cell-cancer study. VI. The role of medical and family history. *Int J Cancer* 1996;66:723-726.
- Chow WH, Devesa SS, Warren JL, Fraumeni JF Jr. Kidney cancer incidence trends in the United States. *JAMA* 1999;281:1628-1631.
- Jin F, Devesa SS, Zheng W, Blot WJ, Fraumeni JF Jr, Gao YT. Cancer incidence trends in urban Shanghai, 1972-1989. *Int J Cancer* 1993;53:764-770.
- McCredie M. Bladder and kidney cancers. In: Doll R, Fraumeni JF Jr, Muir CS, eds. *Cancer surveys: trends in cancer incidence and mortality*. New York: Cold Spring Harbor Laboratory Press, 1994:19/20:343-368.
- Liu S, Semenciw R, Morrison H, Schanzer D, Mao Y. Kidney cancer in Canada: the rapidly increasing incidence of adenocarcinoma in adults and seniors. *Can J Public Health* 1997;8:99-104.
- Brethau D, Lechevallier E, Eghazarian C, Grisoni V, Coulange C. Prognostic significance of incidental renal cell carcinoma. *Eur Urol* 1995;5:319-323.
- Homma Y, Kawabe K, Kitamura T, et al. Increased incidental detection and reduced mortality in renal cancer—recent retrospective analysis at eight institutions. *Int J Urol* 1995;2:77-80.
- Jayson M, Sanders H. Increased incidence of serendipitously discovered renal cell carcinoma. *Urology* 1998;51:203-205.
- McLaughlin JK, Mandel JS, Blot WJ, Schuman LM, Mehl ES, Fraumeni JF Jr. A population-based case-control study of renal cell carcinoma. *J Natl Cancer Inst* 1984;72:275-284.
- Yu MC, Mack TM, Hanisch R, Cicioni C, Henderson BE. Cigarette smoking, obesity, diuretic use, and coffee consumption as risk factors for renal cell carcinoma. *J Natl Cancer Inst* 1986;77:351-356.
- Brownson RC. A case-control study of renal cell carcinoma in relation to occupation, smoking, and alcohol consumption. *Arch Environ Health* 1988;43:238-241.
- McCredie M, Ford JM, Stewart JH. Risk factors for cancer of the renal parenchyma. *Int J Cancer* 1988;42:13-16.

29. McLaughlin JK, Gao YT, Gao RN, et al. Risk factors for renal-cell cancer in Shanghai, China. *Int J Cancer* 1992;52:562-565.
30. McCredie M, Stewart JH. Risk factors for kidney cancer in New South Wales. I. Cigarette smoking. *Eur J Cancer* 1992;28A:2050-2054.
31. Kreiger N, Marrett LD, Dodds L, Hilditch S, Darlington GA. Risk factors for renal cell carcinoma: results of a population-based case-control study. *Cancer Causes Control* 1993;4:101-110.
33. Muscat JE, Hoffmann D, Wynder EL. The epidemiology of renal cell carcinoma: a second look. *Cancer* 1995;75:2552-2557.
34. McLaughlin JK, Lindblad P, Mellemegaard A, et al. International renal-cell cancer study. I. Tobacco use. *Int J Cancer* 1995;60:194-198.
35. Schlehofer B, Heuer C, Blettner M, Niehoff D, Wahrendorf J. Occupation, smoking and demographic factors, and renal cell carcinoma in Germany. *Int J Epidemiol* 1995;24:51-57.
36. Yuan JM, Castela JE, Gago-Dominguez M, Yu MC, Ross RK. Tobacco use in relation to renal cell carcinoma. *Cancer Epidemiol Biomarkers Prev* 1998;7:429-433.
37. Goodman MT, Morgenstern H, Wynder EL. A case-control study of factors affecting the development of renal cell cancer. *Am J Epidemiol* 1986;124:926-941.
38. Asal NR, Geyer JR, Risser DR, Lee ET, Kadamani S, Cherng N. Risk factors in renal cell carcinoma. I. Methodology, demographics, tobacco, beverage use, and obesity. *Cancer Detect Prev* 1988;11:359-377.
39. Talamini R, Barón AE, Barra S, et al. A case-control study of risk factor for renal cell cancer in northern Italy. *Cancer Causes Control* 1990;1:125-131.
40. Benhamou S, Lenfant MH, Ory-Paoletti C, Flamant R. Risk factors for renal-cell carcinoma in a French case-control study. *Int J Cancer* 1993;55:32-36.
41. Siemiatycki J, Krewski D, Franco E, Kaiserman M. Associations between cigarette smoking and each of 21 types of cancer: a multi-site case-control study. *Int J Epidemiol* 1995;24:504-514.
42. McLaughlin JK, Hrubec Z, Blot WJ, Fraumeni JF Jr. Smoking and cancer mortality among U.S. veterans: a 26-year follow-up. *Int J Cancer* 1995;60:190-193.
43. Coughlin SS, Neaton JD, Randall B, Sengupta A. Predictors of mortality from kidney cancer in 332,547 men screened for the Multiple Risk Factor Intervention Trial. *Cancer* 1997;79:2171-2177.
44. Heath CW Jr, Lally CA, Calle EE, McLaughlin JK, Thun MJ. Hypertension, diuretics, and antihypertensive medications as possible risk factors for renal cell cancer. *Am J Epidemiol* 1997;145:607-613.
45. Benichou J, Chow WH, McLaughlin JK, Mandel JS, Fraumeni JF Jr. Population attributable risk of renal cell cancer in Minnesota. *Am J Epidemiol* 1998;148:424-430.
46. Health, United States, 1996-97, and Injury Chartbook. Hyattsville, Maryland: National Center for Health Statistics 1997;182-183.
47. Fraser GE, Phillips R, Beeson WL. Hypertension, antihypertensive medication and risk of renal carcinoma in California Seventh-Day Adventists. *Int J Epidemiol* 1990;19:832-838.
48. Hiatt RA, Tolan K, Quesenberry CP Jr. Renal cell carcinoma and thiazide use: a historical, case-control study (California, USA). *Cancer Causes Control* 1994;5:319-325.
49. McCredie M, Stewart JH. Risk factors for kidney cancer in New South Wales, Australia. II. Urologic disease, hypertension, obesity, and hormonal factors. *Cancer Causes Control* 1992;3:323-331.
50. Mellemegaard A, Engholm G, McLaughlin JK, Olsen JH. Risk factors for renal-cell carcinoma in Denmark. III. Role of weight, physical activity and reproductive factors. *Int J Cancer* 1994;56:66-71.
51. Lindblad P, Wolk A, Bergström R, Persson I, Adami HO. The role of obesity and weight fluctuations in the etiology of renal cell cancer: a population-based case-control study. *Cancer Epidemiol Biomarkers Prev* 1994;3:631-639.
52. Mellemegaard A, Lindblad P, Schlehofer B, et al. International renal-cell cancer study. III. Role of weight, height, physical activity, and use of amphetamines. *Int J Cancer* 1995;60:350-354.
53. Chow WH, McLaughlin JK, Mandel JS, Wacholder S, Niwa S, Fraumeni JF Jr. Obesity and risk of renal cell cancer. *Cancer Epidemiol Biomarkers Prev* 1996;5:17-21.
54. Yuan JM, Castela JE, Gago-Dominguez M, Ross RK, Yu MC. Hypertension, obesity and their medications in relation to renal cell carcinoma. *Br J Cancer* 1998;77:1508-1513.
55. Lew EA, Garfinkel L. Variations in mortality by weight among 750,000 men and women. *J Chron Dis* 1979;32:563-576.
56. Whittemore AS, Paffenbarger RS Jr, Anderson K, Lee JE. Early precursors of urogenital cancers in former college men. *J Urol* 1984;132:1256-1261.
57. Mellemegaard A, Møller H, Olsen JH, Jensen OM. Increased risk of renal cell carcinoma among obese women. *J Natl Cancer Inst* 1991;83:1581-1582.
58. Møller H, Mellemegaard A, Lindvig K, Olsen JH. Obesity and cancer risk: a Danish record-linkage study. *Eur J Cancer* 1994;30A:344-350.
59. Tulinius H, Sigfússon N, Sigvaldason H, Bjarnadóttir K, Tryggvadóttir L. Risk factors for malignant diseases: a cohort study on a population of 22,946 Icelanders. *Cancer Epidemiol Biomarkers Prev* 1997;6:863-873.
60. Prineas RJ, Folsom AR, Zhang ZM, Sellers TA, Potter J. Nutrition and other risk factors for renal cell carcinoma in postmenopausal women. *Epidemiology* 1997;8:31-36.
61. Flegal KM, Carroll MD, Kuczmarski RJ, Johnson CL. Overweight and obesity in the United States: prevalence and trends, 1960-1994. *Int J Obesity* 1998;22:39-47.
62. Kumar A, Mittal S, Buckshee K, Farooq A. Reproductive functions in obese women. *Prog Food Nutr Sci* 1993;17:89-98.
63. Goldfarb S, Pugh TD. Morphology and anatomic localization of renal microneoplasms and proximal tubule dysplasias induced by four different estrogens in the hamster. *Cancer Res* 1990;50:113-119.
64. Weisz J, Fritz-Wolz G, Clawson GA, Benedict CM, Abendroth C, Creveling CR. Induction of nuclear catechol-O-methyltransferase by estrogens in hamster kidney: implications for estrogen-induced renal cancer. *Carcinogenesis* 1998;19:1307-1312.
65. Attia N, Tamborlane WV, Heptulla R, et al. The metabolic syndrome and insulin-like growth factor I regulation in adolescent obesity. *J Clin Endocrinol Metab* 1998;83:1467-1471.
66. Narayan S, Roy D. Insulin-like growth factor I receptors are increased in estrogen-induced kidney tumors. *Cancer Res* 1993;53:2256-2259.
67. Kasiske BL, O'Donnell MP, Keane WF. The Zucker rat model of obesity, insulin resistance, hyperlipidemia, and renal injury. *Hypertension* 1992;19:1110-1115.
68. Huang Z, Willett WC, Manson JE, et al. Body weight, weight change, and risk for hypertension in women. *Ann Intern Med* 1998;128:81-88.
69. Raynor WJ Jr, Shekelle RB, Ross AH, Maliza C, Paul O. High blood pressure and 17-year cancer mortality in the Western Electric Health Study. *Am J Epidemiol* 1981;113:371-377.
70. Goldbourt U, Holtzman E, Yaari S, Cohen L, Katz L, Neufeld HN. Elevated systolic blood pressure as a predictor of long-term cancer mortality: analysis by site and histologic subtype in 10,000 middle-aged and elderly men. *J Natl Cancer Inst* 1986;77:63-70.
71. Asal NR, Lee ET, Geyer JR, Kadamani S, Risser DR, Cherng N. Risk factors in renal cell carcinoma. II. Medical history, occupation, multivariate analysis, and conclusions. *Cancer Detect Prev* 1988;13:263-279.
72. Chow WH, McLaughlin JK, Mandel JS, Wacholder S, Niwa S, Fraumeni JF Jr. Risk of renal cell carcinoma in relation to diuretics, antihypertensive drugs, and hypertension. *Cancer Epidemiol Biomarkers Prev* 1995;4:327-331.
73. Grove JS, Nomura A, Severson RK, Stemmermann GN. The association of blood pressure with cancer incidence in a prospective study. *Am J Epidemiol* 1991;134:942-947.
74. Mellemegaard A, Niwa S, Mehl ES, Engholm G, McLaughlin JK, Olsen JH. Risk factors for renal cell carcinoma in Denmark: Role of medication and medical history. *Int J Epidemiol* 1994;23:923-930.
75. McLaughlin JK, Chow WH, Mandel JS, et al. International renal-cell cancer study. VIII. Role of diuretics, other anti-hypertensive medications and hypertension. *Int J Cancer* 1995;63:216-221.
76. Buck C, Donner A. Cancer incidence in hypertensives. *Cancer* 1987;59:1386-1390.
77. Hole DJ, Hawthorne VM, Isles CG, et al. Incidence of and mortality from cancer in hypertensive patients. *BMJ* 1993;306:609-611.
78. Shapiro JA, Williams MA, Weiss NS, Stergachis A, LaCroix AZ, Barlow WE. Hypertension, antihypertensive medication use, and risk of renal cell carcinoma. *Am J Epidemiol* 1999;149:521-530.
79. Weinmann S, Glass AG, Weiss NS, Psaty BM, Siscovick DS, White E. Use of diuretics and other antihypertensive medications in relation to the risk of renal cell cancer. *Am J Epidemiol* 1994;140:792-804.
80. Steffens J, Bock R, Braedel HU, Isenberg E, Bührle CP, Ziegler M. Renin-producing renal cell carcinomas—clinical and experimental

- investigations on a special form of renal hypertension. *Urol Res* 1992;20:111-115.
81. Federation of American Societies for Experimental Biology, Life Sciences Research Office. Prepared for the Interagency Board for Nutrition Monitoring and Related Research. Third report on nutrition monitoring in the United States, vol 1. Washington: U.S. Government Printing Office; 1995;ES-9-ES-11.
 82. Gross TP, Wise RP, Knapp DE. Antihypertensive drug use. Trends in the United States from 1973 to 1985. *Hypertension* 1989;13[Suppl 1]:1113-1118.
 83. van Zwieten PA. Development and trends in the drug treatment of essential hypertension. *J Hypertension* 1992;10[Suppl 7]:S1-S12.
 84. Møllemegaard A, Møller H, Olsen JH. Diuretics may increase risk of renal cell carcinoma. *Cancer Causes Control* 1992;3:309-312.
 85. Lindblad P, McLaughlin JK, Møllemegaard A, Adami HO. Risk of kidney cancer among patients using analgesics and diuretics: a population-based cohort study. *Int J Cancer* 1993;55:5-9.
 86. McLaughlin JK, Blot WJ, Fraumeni JF Jr. Diuretics and renal cell cancer. *J Natl Cancer Inst* 1988;80:378.
 87. Finkle WD, McLaughlin JK, Rasgon SA, Yeoh HH, Low JE. Increased risk of renal cell cancer among women using diuretics in the United States. *Cancer Causes Control* 1993;4:555-558.
 88. Rosenberg L, Rao S, Palmer JR, et al. Calcium channel blockers and the risk of cancer. *JAMA* 1998;279:1000-1004.
 89. Fahey TP, Peters TJ. What constitutes controlled hypertension? Patient based comparison of hypertension guidelines. *BMJ* 1996;313:93-96.
 90. McLaughlin JK, Blot WJ, Mehl ES, Fraumeni JF Jr. Relation of analgesic use to renal cancer: population-based findings. *Natl Cancer Inst Monogr* 1985;69:217-222.
 91. Maclure M, MacMahon B. Phenacetin and cancers of the urinary tract. *Lancet* 1985;313:1479.
 92. McCredie M, Stewart JH, Carter JJ, Turner J, Mahony JF. Phenacetin and papillary necrosis: independent risk factors for renal pelvis cancer. *Kidney Int* 1986;30:81-84.
 93. U.S. Congress. FDA Notice. *Federal Register* 1983 Oct 5;48(194):45466.
 94. Hinson JA. Reactive metabolites of phenacetin and acetaminophen: a review. *Environ Health Perspect* 1983;50:37-49.
 95. Matson MA, Cohen EP. Acquired cystic kidney disease: occurrence, prevalence, and renal cancers. *Medicine* 1990;69:217-226.
 96. Sasagawa I, Terasawa Y, Imai K, Sekino H, Takahashi H. Acquired cystic disease of the kidney and renal carcinoma in haemodialysis patients: ultrasonographic evaluation. *Br J Urol* 1992;70:236-239.
 97. Chen KS, Lai MK, Huang CC, Chu SH, Leu ML. Urologic cancers in uremic patients. *Am J Kidney Dis* 1995;25:694-700.
 98. Bucciati G, Maisonneuve P, Ravasi B, Cresseri D, Locatelli F, Boyle P. Cancer among patients on renal replacement therapy: a population-based survey in Lombardy, Italy. *Int J Cancer* 1996;66:591-593.
 99. Levine E, Slusher SL, Grantham JJ, Wetzel LH. Natural history of acquired renal cystic disease in dialysis patients: a prospective longitudinal CT study. *AJR Am J Roentgenol* 1991;156:501-506.
 100. Chow WH, Lindblad P, Gridley G, et al. Risk of urinary tract cancers following kidney or ureter stones. *J Natl Cancer Inst* 1997;89:1453-1457.
 101. Rackley RR, Angermeier KW, Levin H, Pontes JE, Kay R. Renal cell carcinoma arising in a regressed multicystic dysplastic kidney. *J Urol* 1994;152:1543-1545.
 102. Hohenfellner M, Schultze-Lampel D, Lampel A, Steinbach F, Cramer BM, Thuroff JW. Tumor in the horseshoe kidney: clinical implications and review of embryogenesis. *J Urol* 1992;147:1098-1102.
 103. Gemperle O, Neuweiler J, Reutter FW, Hildebrandt F, Krapp R. Familial glomerulopathy with giant fibrillar (fibronectin-positive) deposits: 15-year follow-up in a large kindred. *Am J Kidney Dis* 1996;28:668-675.
 104. Adami HO, McLaughlin J, Ekblom A, et al. Cancer risk in patients with diabetes mellitus. *Cancer Causes Control* 1991;2:307-314.
 105. Wideroff L, Gridley G, Møllemegaard L, et al. Cancer incidence in a population-based cohort of patients hospitalized with diabetes mellitus in Denmark. *J Natl Cancer Inst* 1997;89:1360-1365.
 106. Lindblad P, Chow WH, Chan J, et al. The role of diabetes mellitus in the etiology of renal cell cancer. *Diabetologia* 1999;42:107-112.
 107. Kessler II. Cancer mortality among diabetics. *J Natl Cancer Inst* 1970;44:673-686.
 108. La Vecchia C, Negri E, Franceschi S, D'Avanzo B, Boyle P. A case-control study of diabetes mellitus and cancer risk. *Br J Cancer* 1994;70:950-953.
 109. O'Mara BA, Byers T, Schoenfeld E. Diabetes mellitus and cancer risk: a multisite case-control study. *J Chronic Dis* 1985;38:435-441.
 110. Li JJ, Li SA, Klicka JS, Parsons JR, Lam LK. Relative carcinogenicity of various synthetic and natural estrogens in the Syrian hamster kidney. *Cancer Res* 1983;43:5200-5204.
 111. Jakse G, Muller-Holzner E. Hormone receptors in renal cancer: an overview. *Sem Oncol* 1988;4:161-164.
 112. Corté-Vizcaíno V, Llombart-Bosch A. Estrogen and progesterone receptors in the diethylstilbestrol-induced kidney neoplasms of the Syrian golden hamster: correlation with histopathology and tumoral stages. *Carcinogenesis* 1993;14:1215-1219.
 113. Chow WH, McLaughlin JK, Mandel JS, Blot WJ, Niwa S, Fraumeni JF Jr. Reproductive factors and the risk of renal cell cancer among women. *Int J Cancer* 1995;60:321-324.
 114. Lindblad P, Møllemegaard A, Schlehofer B, et al. International renal-cell cancer study. V. Reproductive factors, gynecologic operations and exogenous hormones. *Int J Cancer* 1995;61:192-198.
 115. Chow WH, Gridley G, McLaughlin JK, et al. Protein intake and risk of renal cell cancer. *J Natl Cancer Inst* 1994;86:1131-1139.
 116. Møllemegaard A, McLaughlin JK, Overvad K, Olsen JH. Dietary risk factors for renal cell carcinoma in Denmark. *Eur J Cancer* 1996;32A:673-682.
 117. Yuan JM, Gago-Dominguez M, Castela JE, Hankin JH, Ross RK, Yu MC. Cruciferous vegetables in relation to renal cell carcinoma. *Int J Cancer* 1998;77:211-216.
 118. Wolk A, Gridley G, Niwa S, et al. International renal cell cancer study. VII. Role of diet. *Int J Cancer* 1996;65:67-73.
 119. Wakabayashi K, Totsuka Y, Fukutome K, Oguri A, Ushiyama H, Sugimura T. Human exposure to mutagenic/carcinogenic heterocyclic amines and comutagenic betacarbolines. *Mutat Res* 1997;376:499-503.
 120. Wolk A, Lindblad P, Adami HO. Nutrition and renal cell cancer. *Cancer Causes Control* 1996;7:5-18.
 121. Blot WJ, Chow WH, McLaughlin JK. Tea and cancer: a review of the epidemiologic evidence. *Eur J Cancer Prev* 1996;5:425-438.
 122. Selikoff IJ, Hammond EC, Seidman H. Mortality experience of insulation workers in the United States and Canada, 1943-1976. *Ann NY Acad Sci* 1979;330:91-116.
 123. Enterline PE, Hartley J, Henderson V. Asbestos and cancer: a cohort followup to death. *Am J Ind Med* 1987;44:396-401.
 124. Mandel JS, McLaughlin JK, Schlehofer B, et al. International renal-cell cancer study. IV. Occupation. *Int J Cancer* 1995;61:601-605.
 125. Redmond CK. Cancer mortality among coke oven workers. *Environ Health Perspect* 1983;52:67-73.
 126. Blair A, Decoufle P, Grauman D. Causes of death among laundry and dry cleaning workers. *Am J Public Health* 1979;69:508-511.
 127. Brown DP, Kaplan SD. Retrospective cohort mortality study of dry cleaning workers using perchloroethylene. *J Occup Med* 1987;29:535-541.
 128. McLaughlin JK, Blot WJ, Mehl ES, Stewart PA, Venable FS, Fraumeni JF Jr. Petroleum-related employment and renal cell cancer. *J Occup Med* 1985;27:672-674.
 129. Partanen T, Heikkilä P, Hernberg S, Kauppinen T, Moneta G, Ojajarvi A. Renal cell cancer and occupational exposure to chemical agents. *Scand J Work Environ Health* 1991;17:231-239.
 130. Cocco P, Hua F, Boffetta P, et al. Mortality of Italian lead smelter workers. *Scand J Work Environ Health* 1997;23:15-23.
 131. Band PR, Nhu DL, Fang R, et al. Cohort mortality study of pulp and paper mill workers in British Columbia, Canada. *Am J Epidemiol* 1997;146:186-194.
 132. Sinks T, Lushniak B, Haussler BJ, et al. Renal cell cancer among paperboard printing workers. *Epidemiology* 1992;3:483-489.
 133. Henschler D, Vamvakas S, Lammert M, et al. Increased incidence of renal cell tumors in a cohort of cardboard workers exposed to trichloroethene. *Arch Toxicol* 1995;69:291-299.
 134. Lowery JT, Peters JM, Deapen D, London SJ. Renal cell carcinoma among architects. *Am J Ind Med* 1991;20:123-125.
 135. Brauch H, Weirich G, Hornauer MA, Störkel S, Wöhl T, Brüning T. Trichloroethylene exposure and specific somatic mutations in patients with renal cell carcinoma. *J Natl Cancer Inst* 1999;91:854-861.
 136. Li FP, Decker HJ H, Zbar B, et al. Clinical and genetic studies of renal cell carcinoma in a family with a constitutional chromosome 3;8 translocation. *Ann Int Med* 1993;118:106-111.
 137. Zbar B, Glenn GM, Lubensky I, et al. Hereditary papillary renal cell carcinoma: clinical studies in 10 families. *J Urol* 1995;153:907-912.
 138. Schmidt L, Junker K, Weirich G, et al. Two North American families with hereditary papillary renal carcinoma and identical novel mutations in the MET proto-oncogene. *Cancer Res* 1998;58:1719-1722.

139. Koolen MI, van der Meyden AP, Bodmer D, et al. A familial case of renal cell carcinoma and a t(2;3) chromosome translocation. *Kidney Int* 1998;53:273-275.
140. Glenn GM, Gnarr JR, Choyke PL, Walther MM, Zbar B, Linehan WM. The molecular genetics of renal cell carcinoma. In: Raghavan D, Scher HI, Leibel SA, Lange PH, eds. *Principles and practice of genitourinary oncology*. Philadelphia: Lippincott-Raven Publishers, 1997: 787-794.
141. Latif F, Tory K, Gnarr J, et al. Identification of the von Hippel-Lindau disease tumor suppressor gene. *Science* 1993;260:1317-1320.
142. Gemmill RM, West JD, Boldog F, et al. The hereditary renal cell carcinoma 3;8 translocation fuses *FHIT* to a *patched*-related gene, *TRC8*. *Proc Natl Acad Sci U S A* 1998;95:9572-9577.
143. Schmidt L, Duh FM, Chen F, et al. Germline and somatic mutations in the tyrosine kinase domain of the *MET* proto-oncogene in papillary renal carcinomas. *Nat Genet* 1997;16:68-73.
144. Gnarr JR, Tory K, Weng Y, et al. Mutations of the *VHL* tumour suppressor gene in renal carcinoma. *Nat Genet* 1994;7:85-90.
145. Clifford SC, Prowse AH, Affara NA, Buys CHCM, Maher ER. Inactivation of the von Hippel-Lindau (*VHL*) tumour suppressor gene and allelic losses at chromosome arm 3p in primary renal cell carcinoma: evidence for a *VHL*-independent pathway in clear cell renal tumorigenesis. *Genes Chromosomes Cancer* 1998;22:200-209.
146. Weirich G, Glenn G, Junker K, et al. Familial renal oncocytoma: clinicopathological study of 5 families. *J Urol* 1998;160:335-340.
147. Perera FP. Molecular epidemiology: insights into cancer susceptibility, risk assessment and prevention. *J Natl Cancer Inst* 1996;88:496-509.
148. Caporaso N, Goldstein A. Issues involving biomarkers in the study of the genetics of human cancer. In: Toniolo P, Boffetta P, Shuker DEG, Rothman N, Hulka B, Pearce N, eds. *Application of biomarkers in cancer epidemiology*. IARC Scientific Publications No. 142. Lyon: International Agency for Research on Cancer, 1997;237-250.
149. Rebbeck TR. Molecular epidemiology of the human glutathione S-transferase genotypes *GSTM1* and *GSTT1* in cancer susceptibility. *Cancer Epidemiol Biomarkers Prev* 1997;6:733-743.
150. Brtning T, Lammert M, Kempkes M, Thier R, Golka K, Bolt HM. Influence of polymorphisms of *GSTM1* and *GSTT1* for risk of renal cell cancer in workers with long-term high occupational exposure to trichloroethene. *Arch Toxicol* 1997;71:596-599.
151. Schulz WA, Krummeck A, Rösinger I, et al. Increased frequency of a null-allele for NAD(P)H: quinone oxidoreductase in patients with urological malignancies. *Pharmacogenetics* 1997;7:235-239.