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TOPIC PAPER

Contemporary epidemiology of renal cell carcinoma: perspectives of primary prevention

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Abstract
Objective Epidemiological research of recent years has produced evidence for a role of lifestyle-associated risk factors in the etiology of renal cell carcinoma (RCC), the most common renal tumor. In this review, we give an overview of recent trends in incidence and mortality and summarize the current knowledge on risk factors of RCC.
Methods Data on incidence and mortality in the literature were reviewed. Global incidence data were derived from the Globocan database. A literature review of epidemiological studies on risk factors of kidney cancer was performed, with special emphasis on recent studies with high level of evidence, i.e., meta-analyses and prospective cohort studies.
Results The incidence of renal malignancies has increased over recent decades in the context of the more widespread use of diagnostic imaging. However, time trends and geographic variations in incidence and mortality may also relate to changes in the prevalence of risk factors. Cigarette smoking, excess body weight and uncontrolled blood pressure are the most important and modifiable risk factors for RCC with a high prevalence in the general population. Moreover, dietary habits associated with a Western lifestyle were proposed as potential risk factors, but no food or food group has consistently been related to RCC risk.
Conclusion Based on the current evidence, reductions in the prevalence of cigarette smoking, overweight and hypertension are preventive strategies for RCC. More research is needed to establish the underlying mechanisms linking these risk factors and renal carcinogenesis.

Keywords Epidemiology · Kidney cancer · Risk factor

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Introduction

Renal cell carcinoma (RCC) is the most common renal tumor. Epidemiological research of recent years has produced evidence for a role of a number of lifestyle-associated risk factors in the etiology of this cancer. The incidence and mortality of renal malignancies have increased worldwide over the last 30 years [1], particularly in the Western world where kidney cancer has been among the tumors with the highest upward trend in incidence [1, 2]. Rising incidence rates are partly attributable to improvements in diagnostic imaging, but better detection does not explain the continued high number of advanced tumors and the increase in tumor size-specific mortality among kidney cancer patients [2]. In view of the increasing incidence rates worldwide, the identification of modifiable risk factors may open up perspectives for the primary prevention of RCC.

Trends and variations in global incidence and mortality

Incidence

Worldwide incidence rates are usually reported for kidney cancer. This type of cancer was estimated to be the 14th most common malignancy worldwide in 2002 [3]. More

than 85% of kidney cancers are RCC, with the second most common type being urothelial cell carcinomas of the pelvicaliceal system. It can be assumed that the incidence data of RCC roughly follow those reported for kidney cancer. Reported age-standardized incidence rates vary considerably by geographical region [3], with the highest incidence observed in Europe and northern America [1]. The incidence rates seem to be substantially lower among Asians, both in most Asian countries and the USA [1, 2]. These observations provide indirect evidence that the risk of developing RCC may be higher in whites than Asians, but may also relate to differences in the prevalence of lifestyle-associated risk factors. The lowest incidence rates have been reported from African countries [1], but on the contrary the incidence rates are highest among African Americans in the USA [2]. However, racial as well as geographic disparities in incidence rates may be attributable to differences in frequency of diagnostic imaging, access to health care and prevalence of lifestyle-associated or environmental risk factors. At present, data on an independent association between race and RCC risk is inconclusive.

Age-standardized incidence rates of RCC have generally been reported to be higher among men than women. This pattern is consistently observed throughout the world (Fig. 1) with the exception of Western Africa where reported incidence rates seem to be higher among women [3]. Incidence data, in particular from more developed regions of the world, suggest that men are at an increased risk of developing RCC. A recent analysis of the SEER database has also revealed that men present with significantly larger (6.1 cm vs. 5.9 cm; $P < 0.0001$) and higher grade ($P < 0.0001$) tumors than women [4]. Women with RCC also had significantly improved overall survival: the 5-year survival was 69% for women and 65% for men ($P < 0.0001$). However, cancer-specific survival did not differ significantly between women and men (5-year survival 81% vs. 78%, respectively; $P = 0.960$) [4].

Data from the "Cancer Incidence in Five Continents" database at IARC and the U.S. Surveillance, Epidemiology, and End Results (SEER) Program indicate that incidence rates in Europe and the USA increase consistently with age, with a plateau reached around the age group of 70–75 years and above [5]. The latter effect may be due to less frequent and rigorous diagnostic testing in this age group.

Until recently, the worldwide incidence of RCC has increased by approximately 2% every year. A continued rise in incidence rates was recently confirmed across all age groups and even for all tumor sizes in the USA, based on an analysis of SEER data [6]. However, the most pronounced increase in incidence was noted for localized and very small tumors (<2.0 cm), indicating the effects of more

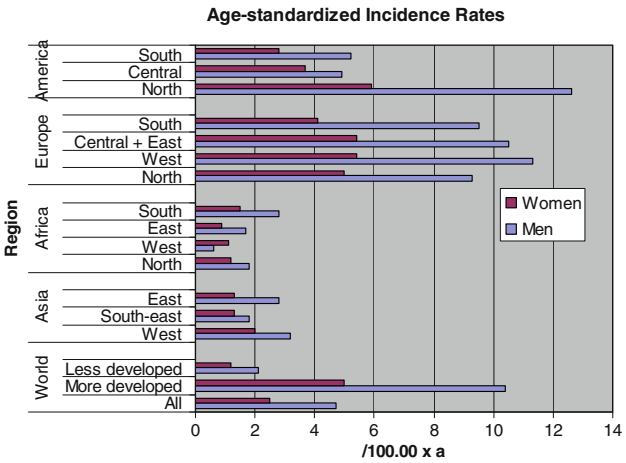

Fig. 1 Age-standardized incidence rates (per 100,000 persons and year) of kidney cancer according to sex and region from the GLOBOCAN database 2002 [3]

widespread use of diagnostic imaging. On the other hand, the continued increase in larger size cancers and among the younger age groups suggests changes in the prevalence of risk factors. According to the recent SEER data, the percentage of RCC diagnosed in the localized stage ranges between 59 and 73% depending on race and sex [6], highlighting that around 30% of cases still present with distant disease at first diagnosis.

In Europe, the situation is more heterogeneous, with regional differences in incidence rates and trends over time. The highest rates are observed in countries of Central and Eastern Europe, whereas relatively low rates are reported from southern Europe. Interestingly, data from a recent European study, which analyzed kidney cancer incidence in 1980–2004, indicate a shift toward stabilization or a decrease in incidence in recent years in both sexes [5]. Recently, also kidney cancer incidence rates have decreased or stabilized in some countries in northern Europe, particularly in Sweden, whereas incidence in Eastern Europe has generally increased (except for women in the early 2000s) [5].

Mortality

Trends of kidney cancer mortality followed the increases of incidence rates in countries of the Western world until recently, although most recent data suggest that mortality rates have leveled off [7]. All-cause mortality rates of patients with kidney cancer in the USA have increased from 1.5/100,000 in 1983 to 6.5/100,000 in 2002 [2]. However, 5-year relative survival has improved over time for patients with kidney cancer from 56.4 (diagnosed in 1983–1987) to 68.9% (diagnosed in 1998–2002), presumably due to the increased proportion of small tumors with a

generally better prognosis [2]. In Europe, overall mortality rates for RCC increased until the late 1980s/early 1990s, and thereafter rates have stabilized or declined in most countries [5, 7]. In the EU, mortality rates from kidney cancer declined from a peak of 4.8/100,000 in 1990–1994 to 4.1/100,000 in 2000–2004 in men, and declined from 2.1 to 1.8/100,000 in women [5]. Increasing rates have been observed in some of the Eastern European countries. The favorable trends in mortality cannot be fully explained by improvements in diagnosis and treatment [5].

Modifiable risk factors

Cigarette smoking

Cigarette smoking has been established as a risk factor for RCC by a large number of studies with a high level of evidence. A meta-analysis [8] including 19 case–control and 5 cohort studies confirmed that ever smokers, i.e., the combined category of former smokers and current smokers, had an increased risk of RCC compared to lifetime never smokers. The increases in risk related to ever smoking were estimated to be 54% for men and 22% for women. The association between smoking and RCC is relatively weak, but a clear dose–response relationship is evident with higher risk estimates with heavier smoking [8]. Apart from the effect of carcinogens contained in tobacco smoke, cigarette smoking may increase RCC risk through chronic tissue hypoxia and lipid peroxidation.

There is only limited evidence to suggest that smoking cessation may reduce the risk of RCC in ever-smoking men after 10 years or longer of non-smoking [8, 9]. Limited data from few case–control studies suggest a potential association between passive smoking, i.e., passive exposure to tobacco smoke among non-smokers, and RCC [9, 10].

Overweight/obesity

Excess body weight has been established as a risk factor for RCC in several case–control and cohort studies. Most studies investigated body mass index (BMI) using self-reported body weight and height. A meta-analysis [11] of prospective studies provided evidence for an association between BMI and risk of RCC with summary risk estimates (per 5 kg/m^2 increase in BMI) of 1.24 in men and 1.34 in women. The results suggested a somewhat stronger association in women than in men, but this difference was not robust. A quantitative review of earlier studies found equally strong associations among men and women. Overall, evidence on sex-specific differences in the association between BMI and RCC risk is not conclusive. A recent investigation in a large European multicenter cohort with detailed information on anthropometric variables and confounding factors confirmed an independent association between BMI and RCC risk in women, but not in men. Studies investigating body fat distribution suggested an increased risk of RCC with increasing waist-to-hip ratio [12–14], but evidence is too limited to conclude that abdominal obesity is a risk factor for RCC independently of BMI or body weight. Limited data suggest an increased risk of RCC with weight gain or weight fluctuations [12, 13, 15].

Blood pressure, hypertension and use of antihypertensive medications

Hypertension or its treatment has been associated with the risk of RCC in several large prospective cohort studies [15–19]. Three cohort [15, 18, 19] and one case–control study [20] measured blood pressure and observed an increased risk of RCC with elevated blood pressure, with a clear dose–response relationship reported in two cohort studies [15, 19]. In one study reporting risk estimates for both sexes combined [19], individuals with systolic ($\geq$160 mmHg) or diastolic ($\geq$100 mmHg) hypertension had more than double the risk compared to individuals with a systolic blood pressure below 120 mmHg and a diastolic blood pressure below 80 mmHg, respectively. The independent contribution of blood pressure level and antihypertensive medication use have generally been difficult to distinguish, as most studies are based on a diagnosis of hypertension that is inevitably linked to treatment with antihypertensive drugs. Data from one case–control study and one adequately powered cohort study indicate that high blood pressure, rather than the use of antihypertensive medication, increases RCC risk [19, 20]. Other studies did not consider blood pressure and medication use independently of each other. Data from two cohort studies suggest that better control of blood pressure may lower RCC risk [15, 19], whereas use of antihypertensive medications including diuretics is probably not a causal risk factor [16, 17, 19, 20]. The association observed between use of diuretics and other antihypertensive drugs may thus be due to confounding by a history of hypertension, but data on this issue remain inconclusive.

Other medical factors

End-stage renal disease, in particular in connection with acquired renal cystic disease (ARCD), is thought to increase the risk of RCC. The incidence of RCC seems to be much higher in ARCD patients than in the general population [21]. However, the independent contribution of ARCD controlling for other important risk factors remains

unclear. Given the relatively low prevalence in the general population, the proportion of RCC cases attributable solely to ARCD will be relatively small.

The role of type 2 diabetes mellitus as a risk factor of RCC is controversial [22], and diabetes may not be associated with RCC risk after adjusting for obesity and hypertension [23]. Use of nonsteroidal anti-inflammatory drugs has not been consistently linked to RCC risk.

Occupational factors

Several occupational risks have been associated with RCC, such as working in iron and steel industry, and blast- or coke-oven industry, and exposure to dry-cleaning solvents, petroleum products and asbestos. However, none of these exposures or occupations has been conclusively associated with RCC risk in large epidemiological studies and, based on the current evidence, RCC cannot be considered an occupation-related cancer [24].

Diet/nutritional factors

Fruits and vegetables

Diets rich in fruits and vegetables contain putative anti-carcinogenic and antimutagenic substances and have been recommended for preventing cancer. However, convincing evidence for a protective role of these dietary components in cancer development is lacking for most malignancies, including RCC. A number of case–control studies reporting on associations between intake of fruits and vegetables and RCC risk have given inconclusive results. Although high fruit and vegetable consumption was associated with a decreased risk of RCC in a pooled analysis of several cohort studies [25], other large prospective cohort studies [19, 26] failed to demonstrate such an association. Altogether, there is no convincing evidence to suggest that high intake of fruit or vegetables may lower the risk of developing RCC.

Foods from animal sources

Geographic variations in incidence and mortality suggest a role for environmental and dietary factors in the etiology of RCC. In particular, dietary habits associated with a Western lifestyle have been proposed as potential risk factors of RCC. Indeed, the consumption of red or processed meat was associated with increased risk of RCC in a meta-analysis of case–control studies [27]. However, this association to risk was not confirmed in a pooled analysis of cohort studies [28], and the role of meat consumption needs to be studied further.

Other food groups including fish, poultry and dairy products could not be consistently linked to the risk of RCC in previous case–control or cohort studies. Interestingly, the risk of RCC was lower among women with high consumption of fatty fish in a Swedish cohort study [29], but this association needs confirmation in other cohort studies.

Alcohol and other beverages

According to recent cohort studies [23, 30], moderate alcohol consumption may lower the risk of RCC compared to non-consumers or heavy alcohol drinking. However, more data from prospective cohort studies is needed to confirm alcohol intake as a risk factor of RCC. Data on other beverages including coffee, tea, soft drinks or juices are not conclusive.

Nutrients

The current evidence, in particular from prospective cohort studies, does not suggest that intake of macronutrients, such as protein and fat, is associated with RCC risk [28, 31]. In a recent Canadian study, intakes of total fat, saturated fat, monosaturated fat, trans fat and cholesterol were all associated with risk of RCC, and fiber intake was inversely associated. However, no associations were observed in prospective cohort studies [28, 31]. The inverse associations between RCC risk and nutrients of plant origin, such as carotenoids [25, 32, 33] and flavonoids [33], deserve further study. Data on vitamin intake and RCC risk have been inconclusive, although a recent case–control study reported that variants in the vitamin D receptor gene may be related to RCC risk [34].

Genetic factors

The genetic background of RCC is illustrated by its association with family history [35]. Having a first-degree relative with kidney cancer is associated with an increased risk of RCC. According to a recent case–control analysis with systematic meta-analysis, a history of RCC in first-degree relatives was associated with a 4.3-fold (95% CI, 1.6–11.9) increase in RCC risk [36]. A family history of kidney cancer was associated with a 2.8-fold (95% CI, 1.0–7.8) increased risk of RCC, and the meta-analysis further confirmed this association, with a 2.2-fold increased risk of RCC (95% CI, 1.6–2.9). A study evaluating familial aggregation among RCC patients in Iceland demonstrated a 2–3-fold increase in RCC risk for first-degree relatives, and a 1.6-fold increased risk for third-degree relatives [37].

Approximately, 2–3% of RCC can be directly attributed to inherited genetic defects. Four familial renal cell carcinoma syndromes have been described (reviewed in Ref. [38]): the von Hippel–Lindau (VHL) syndrome caused by loss of function mutations in the VHL gene and associated with clear-cell RCC, hereditary papillary RCC caused by activating mutations in the c-Met proto-oncogene and associated with type 1 papillary RCC, familial leiomyomatosis and RCC linked to mutations in the fumarate hydratase gene and associated with type 2 papillary RCC, and the Birt–Hogg–Dubé syndrome caused by mutations in the folliculin tumor suppressor gene and associated with chromophobe RCC and oncocytomas, but also other subtypes of RCC. Inherited clear-cell RCC is the most common and best studied of these forms. In addition to its association with inherited clear-cell RCC, the VHL gene is often mutated in sporadic non-inherited RCC.

Conclusions

The incidence of RCC has increased over recent decades in the context of the more widespread use of diagnostic imaging and the increasing prevalence of risk factors. Cigarette smoking, excess body weight according to increases in BMI and hypertension are established modifiable risk factors of RCC increasing the risk independently of each other in both sexes. Elevated blood pressure increases RCC risk, while use of antihypertensive medications per se may not be a risk factor as long as blood pressure is effectively controlled. Smoking, overweight and hypertension may together explain as much as 50% of all RCC cases [39]. Thus, reductions in the prevalence of cigarette smoking, excess body weight and uncontrolled blood pressure are preventive strategies for RCC.

Further research should aim at uncovering the underlying mechanisms explaining the relationship between risk factors, such as overweight and hypertension, and RCC. The hypotheses of increased lipid peroxidation and chronic kidney damage are interesting leads in this context.

Conflict of interest statement There is no conflict of interest.

References

1. Mathew A, Devesa SS, Fraumeni JF Jr, Chow WH (2002) Global increases in kidney cancer incidence, 1973–1992. Eur J Cancer Prev 11:171–178
2. Hollingsworth JM, Miller DC, Daignault S, Hollenbeck BK (2006) Rising incidence of small renal masses: a need to reassess treatment effect. J Natl Cancer Inst 98:1331–1334
3. Ferlay J, Bray F, Pisani P, Parkin DM (2004) GLOBOCAN 2002: cancer incidence, mortality, and prevalence worldwide. IARC Press, Lyon
4. Aron M, Nguyen MM, Stein RJ, Gill IS (2008) Impact of gender in renal cell carcinoma: an analysis of the SEER database. Eur Urol 54:133–140
5. Levi F, Ferlay J, Galeone C, Lucchini F, Negri E, Boyle P et al (2008) The changing pattern of kidney cancer incidence and mortality in Europe. BJU Int 101:949–958
6. Chow WH, Devesa SS (2008) Contemporary epidemiology of renal cell cancer. Cancer J 14:288–301
7. Levi F, Lucchini F, Negri E, La Vecchia C (2004) Declining mortality from kidney cancer in Europe. Ann Oncol 15:1130–1135
8. Hunt JD, van der Hel OL, McMillan GP, Boffetta P, Brennan P (2005) Renal cell carcinoma in relation to cigarette smoking: meta-analysis of 24 studies. Int J Cancer 114:101–108
9. Theis RP, Dolwick Grieb SM, Burr D, Siddiqui T, Asal NR (2008) Smoking, environmental tobacco smoke, and risk of renal cell cancer: a population-based case–control study. BMC Cancer 8:387
10. Hu J, Ugnat AM (2005) Active and passive smoking and risk of renal cell carcinoma in Canada. Eur J Cancer 41:770–778
11. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M (2008) Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet 371:569–578
12. Adams KF, Leitzmann MF, Albanes D, Kipnis V, Moore SC, Schatzkin A et al (2008) Body size and renal cell cancer incidence in a large US cohort study. Am J Epidemiol 168:268–277
13. Luo J, Margolis KL, Adami HO, Lopez AM, Lessin L, Ye W (2007) Body size, weight cycling, and risk of renal cell carcinoma among postmenopausal women: the Women's Health Initiative (United States). Am J Epidemiol 166:752–759
14. Pischon T, Lahmann PH, Boeing H, Tjonneland A, Halkjaer J, Overvad K et al (2006) Body size and risk of renal cell carcinoma in the European Prospective Investigation into Cancer and Nutrition (EPIC). Int J Cancer 118:728–738
15. Chow WH, Gridley G, Fraumeni JF Jr, Jarvholm B (2000) Obesity, hypertension, and the risk of kidney cancer in men. N Engl J Med 343:1305–1311
16. Flaherty KT, Fuchs CS, Colditz GA, Stampfer MJ, Speizer FE, Willett WC et al (2005) A prospective study of body mass index, hypertension, and smoking and the risk of renal cell carcinoma (United States). Cancer Causes Control 16:1099–1106
17. Fryzek JP, Poulsen AH, Johnsen SP, McLaughlin JK, Sorensen HT, Friis S (2005) A cohort study of antihypertensive treatments and risk of renal cell cancer. Br J Cancer 92:1302–1306
18. Vatten LJ, Trichopoulos D, Holmen J, Nilsen TI (2007) Blood pressure and renal cancer risk: the HUNT Study in Norway. Br J Cancer 97:112–114
19. Weikert S, Boeing H, Pischon T, Weikert C, Olsen A, Tjonneland A et al (2008) Blood pressure and risk of renal cell carcinoma in the European prospective investigation into cancer and nutrition. Am J Epidemiol 167:438–446
20. Shapiro JA, Williams MA, Weiss NS, Stergachis A, LaCroix AZ, Barlow WE (1999) Hypertension, antihypertensive medication use, and risk of renal cell carcinoma. Am J Epidemiol 149:521–530
21. Denton MD, Magee CC, Ovuworie C, Mauiyyedi S, Pascual M, Colvin RB et al (2002) Prevalence of renal cell carcinoma in patients with ESRD pre-transplantation: a pathologic analysis. Kidney Int 61:2201–2209
22. Lindblad P, Chow WH, Chan J, Bergstrom A, Wolk A, Gridley G et al (1999) The role of diabetes mellitus in the aetiology of renal cell cancer. Diabetologia 42:107–112

23. Setiawan VW, Stram DO, Nomura AM, Kolonel LN, Henderson BE (2007) Risk factors for renal cell cancer: the multiethnic cohort. Am J Epidemiol 166:932–940
24. Siemiatycki J, Richardson L, Straif K, Latreille B, Lakhani R, Campbell S et al (2004) Listing occupational carcinogens. Environ Health Perspect 112:1447–1459
25. Lee JE, Mannisto S, Spiegelman D, Hunter DJ, Bernstein L, van den Brandt PA et al (2009) Intakes of fruit, vegetables, and carotenoids and renal cell cancer risk: a pooled analysis of 13 prospective studies. Cancer Epidemiol Biomarkers Prev 18:1730–1739
26. George SM, Park Y, Leitzmann MF, Freedman ND, Dowling EC, Reedy J et al (2009) Fruit and vegetable intake and risk of cancer: a prospective cohort study. Am J Clin Nutr 89:347–353
27. Faramawi MF, Johnson E, Fry MW, Sall M, Zhou Y (2007) Consumption of different types of meat and the risk of renal cancer: meta-analysis of case–control studies. Cancer Causes Control 18:125–133
28. Lee JE, Spiegelman D, Hunter DJ, Albanes D, Bernstein L, van den Brandt PA et al (2008) Fat, protein, and meat consumption and renal cell cancer risk: a pooled analysis of 13 prospective studies. J Natl Cancer Inst 100:1695–1706
29. Wolk A, Larsson SC, Johansson JE, Ekman P (2006) Long-term fatty fish consumption and renal cell carcinoma incidence in women. JAMA 296:1371–1376
30. Lee JE, Hunter DJ, Spiegelman D, Adami HO, Albanes D, Bernstein L et al (2007) Alcohol intake and renal cell cancer in a pooled analysis of 12 prospective studies. J Natl Cancer Inst 99:801–810
31. Allen NE, Roddam AW, Sieri S, Boeing H, Jakobsen MU, Overvad K et al (2009) A prospective analysis of the association between macronutrient intake and renal cell carcinoma in the European Prospective Investigation into Cancer and Nutrition. Int J Cancer 125:982–987
32. Hu J, La Vecchia C, Negri E, Desmeules M, Mery L (2009) Dietary vitamin C, E, and carotenoid intake and risk of renal cell carcinoma. Cancer Causes Control 20:1451–1458
33. Bosetti C, Scotti L, Maso LD, Talamini R, Montella M, Negri E et al (2007) Micronutrients and the risk of renal cell cancer: a case–control study from Italy. Int J Cancer 120:892–896
34. Karami S, Brennan P, Rosenberg PS, Navratilova M, Mates D, Zaridze D et al (2009) Analysis of SNPs and haplotypes in vitamin D pathway genes and renal cancer risk. PLoS One 4:e7013
35. Gago-Dominguez M, Yuan JM, Castelao JE, Ross RK, Yu MC (2001) Family history and risk of renal cell carcinoma. Cancer Epidemiol Biomarkers Prev 10:1001–1004
36. Clague J, Lin J, Cassidy A, Matin S, Tannir NM, Tamboli P et al (2009) Family history and risk of renal cell carcinoma: results from a case–control study and systematic meta-analysis. Cancer Epidemiol Biomarkers Prev 18:801–807
37. Gudbjartsson T, Jonasdottir TJ, Thoroddsen A, Einarsson GV, Jonsdottir GM, Kristjansson K et al (2002) A population-based familial aggregation analysis indicates genetic contribution in a majority of renal cell carcinomas. Int J Cancer 100:476–479
38. Linehan WM, Vasselli J, Srinivasan R, Walther MM, Merino M, Choyke P et al (2004) Genetic basis of cancer of the kidney: disease-specific approaches to therapy. Clin Cancer Res 10:6282S–6289S
39. Benichou J, Chow WH, McLaughlin JK, Mandel JS, Fraumeni JF Jr (1998) Population attributable risk of renal cell cancer in Minnesota. Am J Epidemiol 148:424–430