Original Article

Risk factors of renal cell carcinoma in a cohort of Sri Lankan patients: A case–control study

Balasingam Balagobi, Kalhar Indika, W. Muditha C. K. Samaraweera[1], K. Suranga N. Wijayarathna, Hansika P. Maddumage[2], Kugadas Sutharshan, Swarna Suvendran, Anuruddha M. Abeygunasekera

Departments of Urology, [1]Radiology and [2]Pathology, Colombo South Teaching Hospital, Dehiwala, Sri Lanka

For correspondence: Dr. Balasingam Balagobi, Department of Urology, Colombo South Teaching Hospital, Dehiwala, Sri Lanka. E-mail: b.balagobi@yahoo.com

ABSTRACT

Background: Associated risk factors for renal cell carcinoma (RCC) include smoking, obesity, hypertension, and diabetes mellitus (DM). Studies on their role in Sri Lankan patients are sparse. The aims were to determine the risk factors for RCC in a cohort of Sri Lankan patients.

Methods: A hospital-based case–control study was done in a teaching hospital from January 1, 2009, to December 31, 2015. The prospectively collected data included history of smoking, hypertension, DM, and body mass index (BMI). The controls were patients who were admitted after trauma and who required abdominal ultrasonography as part of routine assessment. The controls were accrued at a ratio of 1:2 and were age- and gender-matched. Chi-squared test was used, and $P < 0.05$ was considered statistically significant.

Results: There were 178 patients with RCC. The mean age of patients with RCC was 56.9 years. Male to female ratio was 3.5:1. Forty-nine (27.5%) patients were < 50-year-old. 36.5% were asymptomatic and diagnosed incidentally by ultrasound scanning. Obesity (BMI > 30) ($P < 0.01$), DM ($P < 0.05$), and hypertension ($P < 0.01$) were significantly more common among the cases than in controls. There was no difference in the prevalence of smoking between the two groups ($P > 0.5$).

Conclusions: Average age at the time of diagnosis of RCC in Sri Lankan patients is lower than the developed world, with a large proportion of patients being under 50 years. Obesity, hypertension, and DM are associated risk factors for RCC in Sri Lankan patients while smoking is not.

KEY WORDS: Diabetes mellitus, hypertension, obesity, renal cell carcinoma, risk factors, smoking

INTRODUCTION

Asia is the largest continent in the world with countries showing a wide diversity of sociocultural behavior, economic performance, and health-care systems. Sri Lanka is an island nation in South Asia, a developing country with a lower-middle-income economy. Total health expenditure as a share of GDP in Sri Lanka is approximately 3.5%.[1] Twenty-six urological surgeons serve the country's population of 20 million. With universal health care and a robust public health network across the country, Sri Lanka has made noteworthy achievements in health outcomes compared to other developing countries.[2] Sri Lanka is a characteristic of high life expectancy, low maternal and child mortality, and decreasing levels of communicable diseases. While this success is laudable, the country needs to strengthen the existing health system to face changes brought by demographic and epidemiological transitions. Rising incidence of cancer has become a major challenge faced by Sri Lanka.[3]

Renal cell carcinoma (RCC) is a relatively common malignancy accounting for 2–3% of adult malignancies.[4] Worldwide, renal cancer is the 13th most common malignancy, with approximately 271,000 new cases diagnosed in each year.[5] The incidence of renal cancer varies geographically. Rates of renal cancer are highest in Europe, North America, and Australia, whereas rates are low in India, Japan, Africa, and China. Although an increase in RCC has been observed globally; in recent years, the incidence of RCC has declined in some European countries, namely, Sweden,

Cite this article as: Balagobi B, Indika K, Samaraweera WC, Wijayarathna KN, Maddumage HP, Sutharshan K, *et al*. Risk factors of renal cell carcinoma in a cohort of Sri Lankan patients: A case–control study. J Can Res Ther 0;0:0.

Access this article online

Website: www.cancerjournal.net

DOI: 10.4103/0973-1482.206867

Quick Response Code:

Poland, Finland, and the Netherlands.[6] The crude incidence in Sri Lanka is 0.53/100,000 population according to latest available statistics of the National Cancer Registry for the year 2007 in which 106 new cases of renal cancer had been reported.[3] The incidence in Japan is 8.2 and 3.6/100,000 men and women, respectively in 2002.[7] It has been shown that the Sri Lankan National Cancer Registry data are unreliable since it is based on patients registered at oncology units.[8-10] Therefore, the incidence of RCC in Sri Lanka is likely to be higher than reported in the National Cancer Registry.

Several risk factors for RCC have been identified. However, the behavior of RCC differs in different countries.[11] Variation of risk factors in different countries is the likely reason for these differences. Hence, it is important to recognize risk factors that are involved in the local setting to plan and implement prevention strategies to curtail the rising incidence of RCC in developing countries like Sri Lanka. There are genetic and familial syndromes which are well known to be associated with RCC.[12] In addition smoking, obesity and hypertension are well established as associated risk factors for RCC.[11] No large-scale, prospective studies are available with regard to RCC in Sri Lanka. Hence, risk factors, clinicopathological characteristics and treatment trends of RCC in Sri Lanka are unknown.

The incidence of hypertension, diabetes mellitus (DM), and obesity has been increasing rapidly in Sri Lanka in the recent past.[13,14] The prevalence of smoking in Sri Lanka is about 31% among adult men.[2] Therefore, it is important to know whether obesity, hypertension, DM, and smoking are actually associated with a high risk of developing RCC in Sri Lankan patients.

The main objective of our study was to identify risk factors for RCC among a cohort of Sri Lankan patients. We also aimed to describe the clinicopathological characteristics and primary treatment given to patients with RCC in a urology unit of a tertiary care hospital in Sri Lanka.

METHODS

This is a hospital-based case–control study. In the urology unit of a Teaching Hospital in Sri Lanka, a comprehensive cancer registry, and a database are maintained. Adult patients who had treatment for histologically confirmed RCC in a Urology Unit at a Teaching Hospital from January 1, 2009, to December 31, 2015, constituted the cases of this study. The data related to demography, smoking, hypertension, DM, height, weight, calculated body mass index (BMI), and relevant investigations were recorded prospectively in a data sheet.

The controls were patients who got admitted to the hospital after minor traumatic injuries and who required abdominal ultrasonography as part of routine assessment. The controls were accrued at a ratio of 1:2 and were age- and gender-matched. Their height, weight, and blood pressure were measured. History of taking treatment for hypertension and DM and smoking was recorded after taking informed written consent. Their blood sugar level was assessed as part of routine patient evaluation.

All patients with renal tumors had a contrast-enhanced computerized tomography (CT) of the kidneys, ureters, bladder if serum creatinine was below 150 μmol/l to characterize the lesion. Depending on the nephrometry score,[15] age, existing comorbidities, advice of oncologists and patient's wish, decisions were taken to perform partial or radical nephrectomy. Those who were selected for radio-frequency ablation (RFA) or were not fit enough for surgery but opted to have interferon alpha or tyrosine kinase inhibitors had ultrasound-guided core biopsy to confirm the histology.

The smoking status was categorized using the Center for Disease Control and Prevention, Atlanta, USA, classification as active, former, or never.[16] The second-hand exposure was not included in the analysis. Obesity was determined according to the World Health Organization (WHO) classification and BMI of 30 or more were considered as obese.[17] Diastolic blood pressure over 90 mmHg and requiring antihypertensive treatment as recommended by a physician or those already receiving antihypertensive drugs were categorized as having hypertension. Fasting venous plasma glucose level more than 7 mmol/l or being on treatment for DM was considered as having DM. Histopathological evaluation was done according to the WHO and the International Society of Urological Pathology classification 2004.[18] Tumor grading was based on the Fuhrman grading system.[19] Tumor staging was done using the tumor-node metastasis classification of the Union for International Cancer Control 2009.[20] Chi-squared test was used for the statistical analysis, and $P < 0.05$ was considered statistically significant. Approval for the study was obtained from the Ethics Review Committee of the institute.

RESULTS

During the study period, 188 patients with renal tumors were treated in the unit. Distribution of the tumors according to histological diagnosis is given in [Table 1]. There were 178 patients with histologically confirmed RCC. These 178 patients were included in the study sample and analysis as cases. Among the patients with RCC, there were 138 males with a male to female ratio of 3.5:1 [Table 2]. The mean age of patients with RCC was 56.9 years (range: 18–84).There was no significant difference between mean age for male patients (57 years) and for female patients (56.7 years). Table 2 shows the age distribution of the patients and 27.5% were below the age of 50 years. Tumor was detected incidentally during abdominal ultrasonography for other reasons in 65 (38.7%) patients [Table 2].

Surgery was performed in 168 patients [Table 2]. Radical nephrectomy was performed in 125 patients while 42 patients had partial nephrectomy. In one patient, the tumor was

considered inoperable and resectional surgery abandoned after taking a biopsy of the lesion. In ten patients, the diagnosis was made by ultrasound-guided core biopsy of the tumor. Three patients had RFA, two patients had interferon alpha, and one patient had tyrosine kinase inhibitor – sorafenib as the primary treatment. Four patients decided to have symptomatic treatment only, due to varying reasons. There were 7 (3.9%) patients with tumor thrombus extending to the inferior vena cava. Two of them had supradiaphragmatic extensions necessitating synchronous open heart surgery.

Table 1: Histological types of all renal tumors treated during the study period

	n (%)
Renal cell tumors	
Oncocytoma	5 (3)
Clear cell renal cell carcinoma	144 (76.5)
Multilocular cystic clear cell renal neoplasm of low malignant potential	2 (1)
Papillary renal cell carcinoma type 1	8 (4)
Papillary renal cell carcinoma type 2	18 (10)
Chromophobe renal cell carcinoma	4 (2)
Xp11 translocation renal cell carcinoma	1 (0.5)
Renal cell carcinoma unclassified	1 (0.5)
Nephroblastic tumors	
Nephroblastoma (adult Wilms tumor)	2 (1)
Mesenchymal tumors	
Angiomyolipoma (atypical)	1 (0.5)
Solitary fibrous tumor	1 (0.5)
Neuroendocrine tumors	
Neuroendocrine carcinoma	1 (0.5)
Total	188 (100)

Table 2: Characteristics of the 178 patients with renal cell carcinoma

Characteristic	*n* (%)
Age at diagnosis (years), mean	56.9
Gender, *n* (%)	
Male	138 (77.5)
Female	40 (22.5)
Presence of symptoms, *n* (%)	
Symptomatic	113 (63.5)
Asymptomatic	65 (36.5)
Age group (years), *n* (%)	
<20	2 (1.1)
21-30	4 (2.2)
31-40	11 (6.2)
41-50	32 (18)
51-60	40 (22.5)
61-70	60 (33.7)
71-80	24 (13.5)
>80	5 (2.8)
T stage, *n* (%)	
T_{1a}	47 (26.4)
T_{1b}	37 (20.8)
T_2	40 (22.5)
T_3	41 (23)
T_4	3 (1.7)
Missing data	10 (5.6)
M stage, *n* (%)	
M_0	156 (87.6)
M_1	22 (12.4)
N stage, *n* (%)	
N_0	171 (96.1)

We recruited age- and gender-matched 356 controls (280 males and 76 females) for this study. Table 3 shows data related to height, weight, and BMI of cases and controls. The mean BMI in cases was 24.5 kg/m^2 and in controls, it was 22.5 kg/m^2. The distribution of comorbidities among cases and controls is shown in Table 4. Obesity defined as BMI > 30 ($P < 0.01$), DM ($P < 0.05$), and hypertension ($P < 0.01$) were more common among the cases than in controls [Figure 1]. There was no significant difference in the incidence of smoking between the two groups ($P > 0.05$).

Distribution of the tumor stage as determined after histopathological examination and appropriate investigation workup is given in Table 2. Twenty-two (12.4%) patients had metastases at the time of diagnosis. Bone was the most common site of metastases ($n = 11$) while lungs ($n = 9$), liver ($n = 5$), and adrenal glands ($n = 3$) followed.

DISCUSSION

Age at the time of diagnosis in our patients was 56.9 years compared to 67 years in Sweden and 63.9 years in Japan.[21,22]

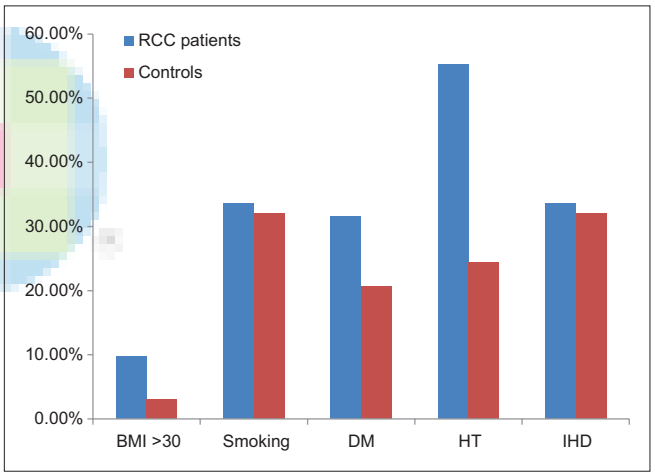

Figure 1: Distribution of evaluated risk factors (%)

Table 3: Anthropometric characteristics of study participants

Measurement	Mean (SD)	
	Cases	Controls
Height (cm)	161.4 (8.7)	160 (8.2)
Weight (kg)	64.1 (13.2)	58.6 (12.5)
BMI (kg/m^2)	24.5 (4.4)	22.5 (4.1)

BMI=Body mass index, SD=Standard deviation

Table 4: Distribution of different risk factors

Comorbidity	Cases (*n*=178)	Controls (*n*=356)	*P*
BMI >30	19	10	<0.01
Smokers	61	120	>0.5
DM	56	76	<0.05
Hypertension	100	86	<0.01

DM=Diabetes mellitus, BMI=Body mass index

In India too, the median age at the time of diagnosis is 56 years.[23] In Japan, only 13% are below 50 years while in our study, cohort 27.5% of the patients were below 50 years. In India, 30.8% are below 50 years.[23] Incidence in Europe and the USA increases consistently with age, with a plateau reaching around 70–75 years.[24] Our study shows that oldest age categories have a considerably lower risk than the somewhat younger categories. It is interesting to note that highest male to female ratio is seen in our study cohort (3.5:1). It is 1.6:1 in Sweden and 2.5:1 in Japan. However, the male to female ratio of our study is closer to that of India (2.9). This high male preponderance cannot be attributed to the rarity of smoking among women in Sri Lanka, as smoking has been shown not to be a risk factor in our study. These differences in mean age and gender distribution raise the possibility of hitherto unidentified risk factors for RCC in Sri Lanka and India.

The distribution of the stage of the disease at the time of diagnosis varies in different countries. In Japan, half the cases are diagnosed at the pT_{1a} stage while it is 28% in our study and 29% in Sweden.[21,22] The same trend is seen with pT_2 and pT_3 stage tumors too. Stage pT_{1b} and pT_4 tumors constitute approximately similar proportions in all three countries. In Japan, 73.2% of RCCs are diagnosed incidentally, whereas the corresponding value in our study is 38.7%.[21] This may be due to the lack of widespread CT facilities in Sri Lanka. In Japan, there are 101.2 CT scanners per million population when the corresponding figure for Sri Lanka is 1.2.[2] Compared to the developed world, prostate and bladder cancers are diagnosed at an advanced stage of the disease in Sri Lanka.[9,10] However, stage of the disease at the time of diagnosis of RCC in Sri Lanka appears to be closer to developed countries. This may be due to the increasing the use of abdominal ultrasonography, which is a relatively cheaper investigation as a diagnostic tool in Sri Lanka in comparison to prostate cancer screening. This suggests the potential in promoting abdominal ultrasonography in other developing countries too, where RCCs are still diagnosed at an advanced stage. The proportion of patients with RCC having metastases at the time of diagnosis in our study (12.3%) is similar to those of Japan (11–12.7%) and Sweden (16%). Even the proportion of pT_3 stage disease in our study and distribution of nodal stage are on par with Sweden and Japan. However, the proportion of metastatic disease at the time of diagnosis of RCC has remained constant over the years, and this may be due to the inability of the existing diagnostic and screening tools such as abdominal ultrasonography and CT to detect aggressive RCCs early.[25]

Compared to Japanese studies (5–8%), our study (14.5%) shows a much higher proportion of papillary RCCs.[21,25] In India, it is 9.8%, and according to a study from Australia, the incidence of papillary RCC has increased steadily over a period of 15 years to reach 13%.[26] The proportion of clear cell carcinomas in an Indian study is only 67.7% compared to 82% of our study and 88% in the Japanese study.[23] The low incidence of clear cell carcinomas in the Indian study may be related to having sarcomatoid malignancies as a separate entity. During the recent past, Fuhrman grade 3 (G3) tumors among RCCs has increased gradually from 17.6% to 30.8% in Australia and 4%–13% in Japan.[25,26] Same trends have been noted in Europe too.[27] The rate of G3 tumors in Sweden is 26%.[22] In our study, G2 tumors still predominate (55.6%) with only 10.7% being G3. The possible reasons for these changes are only speculative including changes in pathological assessment.[25-27]

Radical and partial nephrectomy rates in our study (74.8% and 25%, respectively) are similar to those of Sweden (74% and 23%, respectively).[21,22] The number of laparoscopic nephrectomies has increased gradually in Sweden and Japan, during the recent past.[21,22] Few centers in Sri Lanka perform laparoscopic nephrectomy; however, in our unit, open surgery remains the standard form of nephrectomy.

Excess body weight has been established as a risk factor for RCC in several case–control and cohort studies. A meta-analysis 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.[28] The results suggested a somewhat stronger association in women than in men. The studies investigating body fat distribution suggested an increased risk of RCC with increasing waist-to-hip ratio.[29,30] Our study too provided strong evidence to support that BMI >30 is a risk factor for RCC ($P < 0.01$).

Hypertension or its treatment has been associated with the risk of RCC in several large prospective cohort studies.[31,32] Better control of blood pressure may lower RCC risk, whereas use of antihypertensive medications, including diuretics, is probably not a causal risk factor.[31,32] Similarly, hypertension was an associated risk factor of RCC patients in our study ($P < 0.01$).

Type 2 DM is known to be associated with an increased risk of several cancers. However, a recent epidemiologic study from Italy did not find significant odds ratios between DM and RCC. It concluded that being overweight and obesity are weakly associated with RCC.[33] According to the results of our study, DM was an associated risk factor of RCC ($P < 0.05$). Similar to other South Asian countries, Sri Lanka is facing an expanding epidemic of DM. Steps to control the diabetic epidemic in Sri Lanka will have a beneficial effect on rising incidence of RCC too.

Cigarette smoking is an established risk factor for RCC. A meta-analysis including 19 case–control and five cohort studies confirmed that ever smoking increases the risk of RCC compared to never smoking.[34] The association between smoking and RCC is relatively weak, but a clear dose-response relationship is evident with higher risk estimates associated with heavier smoking. According to our study, smoking was not a risk factor for RCC. It may be that the large proportion

of younger patients with RCC in the cohort played a role for the effect of smoking not to be evident in this sample. A larger sample which will have adequate numbers of older patients may show different results as it may help to pass the threshold level of the dose-response relationship of smoking and RCC.[35]

The substantial worldwide variation in RCC incidence and the increasing rates in Asia, coinciding with dramatic changes in food supply and dietary patterns, suggest that lifestyle, especially diet, plays a role in RCC development.[36] An ecologic study has reported that the per capita daily intakes of fat and proteins are positively correlated with the incidence of kidney cancer in both men and women.[37] A pooled analysis of 13 cohort studies found that fruit and vegetable consumption were associated with a lower risk of RCC.[38] We have not studied those risk factors in our study.

There are few limitations of our study. This study has been conducted in a single urology unit of the country. This sample is inadequate to extrapolate the results to the entire population. The results could be skewed due to small number of cases in groups with different risk factors. We have not analyzed other potential risk factors such as genetic abnormalities, exposure to chemicals including agro-chemicals, and nutritional factors. However, within these limitations, we have analyzed a reasonably large cohort in a country where there is no published data about RCC available for researchers and policy planners. The overall prevalence of hypertension and DM in the general population of Sri Lanka is 28.5% and 18.6%.[2,13,14] These values are in par with the corresponding values (24.2% and 21.3%, respectively) in our age- and gender-matched control group indicating the robustness of our data. The rate of smokers in Sri Lanka, according to WHO statistics, is 31% which is in par with the rate of 33% in our control group.[2] This again supports the validity of our data.

CONCLUSIONS

Obesity, DM, and hypertension are risk factors for the development of RCC in Sri Lanka, while smoking is not. Further studies are necessary to identify reasons for the lower average age at the time of diagnosis and high male to female ratio among patients with RCC in Sri Lanka. Compared to other urological malignancies, RCCs are diagnosed at an early stage in Sri Lanka, somewhat similar to the situation in developed nations. Sri Lanka which is facing a rapidly growing epidemic of obesity, DM, and hypertension may ultimately benefit more from preventive community health interventions than innovations in clinical care for RCC.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Kelegama S, Weerakoon D, Senaratne A, Arunatilake N, Wijayasiri J. Sri Lanka State of the Economy 2015. Srilanka: Institute of Policy Studies of Sri Lanka; 2015
2. World Health Statistics 2014, World Health Organization. Geneva 27, Switzerland: World Health Organization; 2014.
3. Paranagama N, Fernando E, Perera S, Amarasingha H, Jayanth N, Seneviratna K, *et al.* Cancer Incidence Data: Sri Lanka Year 2007. National Cancer Control Programme; 2013.
4. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, *et al.* Cancer statistics, 2008. CA Cancer J Clin 2008;58:71-96.
5. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010;127:2893-917.
6. Karim-Kos HE, de Vries E, Soerjomataram I, Lemmens V, Siesling S, Coebergh JW. Recent trends of cancer in Europe: A combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s. Eur J Cancer 2008;44:1345-89.
7. Marumo K, Kanayama H, Miyao N, Nakazawa H, Ozono S, Horie S, *et al.* Prevalence of renal cell carcinoma: A nation-wide survey in Japan, 2002. Int J Urol 2007;14:479-82.
8. de Silva MV, Fernando MS, Goonewardene SA. Prostatic carcinoma in Sri Lanka – is it more common than cancer registry statistics? Ceylon Med J 1999;44:192.
9. Abeygunasekera AM, Wijayarathna SN, de Silva K, Gobi U, Swarna S, Sujeeva W. Clinicopathological characteristics and primary treatment of prostate cancer in a urology unit of Sri Lanka. J Cancer Res Ther 2015;11:780-5.
10. Sasikumar S, Wijayarathna KS, Karunaratne KA, Gobi U, Pathmeswaran A, Abeygunasekera AM. Pathological characteristics of primary bladder carcinoma treated at a tertiary care hospital and changing demographics of bladder cancer in Sri Lanka. Adv Urol 2015;2015:5751647.
11. Ljungberg B, Campbell SC, Choi HY, Jacqmin D, Lee JE, Weikert S, *et al.* The epidemiology of renal cell carcinoma. Eur Urol 2011;60:615-21.
12. Linehan WM, Pinto PA, Bratslavsky G, Pfaffenroth E, Merino M, Vocke CD, *et al.* Hereditary kidney cancer: Unique opportunity for disease-based therapy. Cancer 2009;115 10 Suppl: 2252-61.
13. Katulanda P, Jayawardena MA, Sheriff MH, Constantine GR, Matthews DR. Prevalence of overweight and obesity in Sri Lankan adults. Obes Rev 2010;11:751-6.
14. Katulanda P, Rathnapala DA, Matthews DR. Prevalence of diabetes among Sri Lankan adults. Sri Lanka J Diab Endocrinol Metabol 2012;1:2-7.
15. Kutikov A, Uzzo RG. The R.E.N.A.L. nephrometry score: A comprehensive standardized system for quantitating renal tumor size, location and depth. J Urol 2009;182:844-53.
16. Albright VA, Mirza S, Caraballo R, Niare A, Thorne SL. Guidance Document for Administrating the Alaska Native Adult Tobacco Survey. U.S. Department of Health and Human Services, Centres for Disease Control and Prevention; 2010.
17. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157-63.
18. Eble JN, Sauter G, Epstein JI, Sesterhenn IA. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs. Lyon: IARC Press; 2004. p. 90.
19. Fuhrman SA, Lasky LC, Limas C. Prognostic significance of morphologic parameters in renal cell carcinoma. Am J Surg Pathol 1982;6:655-63.
20. Sobin LH, Gospodariwicz M, Wittekind C, editors. TNM Classification of Malignant Tumours. 7th ed. New York, USA: Wiley-Blackwell; 2009.
21. Kanayama HO, Fukumori T, Fujimoto H, Nakanishi H, Ohyama C, Suzuki K, *et al.* Clinicopathological characteristics and oncological outcomes in patients with renal cell carcinoma registered in 2007: The first large-scale

multicenter study from the Cancer Registration Committee of the Japanese Urological Association. Int J Urol 2015;22:S1-7.
22. Thorstenson A, Harmenberg U, Lindblad P, Holmström B, Lundstam S, Ljungberg B. Cancer characteristics and current treatments of patients with renal cell carcinoma in Sweden. Biomed Res Int 2015;2015:456040.
23. Agnihotri S, Kumar J, Jain M, Kapoor R, Mandhani A. Renal cell carcinoma in India demonstrates early age of onset and a late stage of presentation. Indian J Med Res 2014;140:624-9.
24. Chow WH, Devesa SS. Contemporary epidemiology of renal cell cancer. Cancer J 2008;14:288-301.
25. Toshio T, Tsunenori K, Kazunari T. Stage migration of renal cell carcinoma at a single Japanese university hospital: 24-year study. Int J Urol 2014;21:429-33.
26. Doeuk N, Guo DY, Haddad R, Lau H, Woo HH, Bariol S, *et al.* Renal cell carcinoma: Stage, grade and histology migration over the last 15 years in a large Australian surgical series. BJU Int 2011;107:1381-5.
27. Pichler M, Hutterer GC, Chromecki TF, Jesche J, Kampel-Kettner K, Eberhard K, *et al.* Trends of stage, grade, histology and tumour necrosis in renal cell carcinoma in a European centre surgical series from 1984 to 2010. J Clin Pathol 2012;65:721-4.
28. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: A systematic review and meta-analysis of prospective observational studies. Lancet 2008;371:569-78.
29. Adams KF, Leitzmann MF, Albanes D, Kipnis V, Moore SC, Schatzkin A, *et al.* Body size and renal cell cancer incidence in a large US cohort study. Am J Epidemiol 2008;168:268-77.
30. Pischon T, Lahmann PH, Boeing H, Tjønneland A, Halkjaer J, Overvad K, *et al.* Body size and risk of renal cell carcinoma in the European prospective investigation into cancer and nutrition (EPIC). Int J Cancer 2006;118:728-38.
31. Chow WH, Gridley G, Fraumeni JF Jr., Järvholm B. Obesity, hypertension, and the risk of kidney cancer in men. N Engl J Med 2000;343:1305-11.
32. Weikert S, Boeing H, Pischon T, Weikert C, Olsen A, Tjonneland A, *et al.* Blood pressure and risk of renal cell carcinoma in the European prospective investigation into cancer and nutrition. Am J Epidemiol 2008;167:438-46.
33. Zucchetto A, Dal Maso L, Tavani A, Montella M, Ramazzotti V, Talamini R, *et al.* History of treated hypertension and diabetes mellitus and risk of renal cell cancer. Ann Oncol 2007;18:596-600.
34. Hunt JD, van der Hel OL, McMillan GP, Boffetta P, Brennan P. Renal cell carcinoma in relation to cigarette smoking: Meta-analysis of 24 studies. Int J Cancer 2005;114:101-8.
35. Hill AB. The environment and disease: Association or causation? Proc R Soc Med 1965;58:295-300.
36. Chow WH, Dong LM, Devesa SS. Epidemiology and risk factors for kidney cancer. Nat Rev Urol 2010;7:245-57.
37. Armstrong B, Doll R. Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. Int J Cancer 1975;15:617-31.
38. Lee JE, Männistö S, Spiegelman D, Hunter DJ, Bernstein L, van den Brandt PA, *et al.* Intakes of fruit, vegetables, and carotenoids and renal cell cancer risk: A pooled analysis of 13 prospective studies. Cancer Epidemiol Biomarkers Prev 2009;18:1730-9.