A CASE CONTROLLED STUDY OF ACQUIRED RISK FACTORS FOR RENAL CELL CARCINOMA IN A SOUTH ASIAN COHORT – IS IT SIMILAR TO THE WEST?

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Abstract

Objective: To identify the validity of established western risk factors in renal cell carcinoma in Sri Lanka.

Design, setting and methods: A case control study was designed to compare 36 consecutive, renal cell carcinoma (RCC) cases treated at one urology unit of a tertiary referral centre with 72 age, sex matched controls. Well studied risk factors in western countries such as smoking, hypertension, obesity, occupational chemical exposure and use of long term analgesics were included. Data was analyzed with standard matched pair methods. Conditional logistic regression models were used to examine the univariate and multivariate relationships of RCC with various risk factors.

Results: There were 28 males and 08 females. Mean age at diagnosis was 56.92 (27-83) years.

Obesity (BMI ≥ 30 kg/m2) increased the risk of RCC by 6 folds in comparison to BMI less than 25. Positive occupational exposure was shown to increase the risk of RCC by 3.2 folds (CI = 1.2-8.5) and hypertension by 4.1 folds (95%CI 1.09 - 15.39) after making adjustments for co-founding factors. Interestingly amount of smoking calculated in pack years showed an increasing trend in the odds ratio suggesting increase risk of RCC with smoking, but failed to show a strong association in the univariate analysis.

Conclusions: Comparing to the results of western studies present smoking state didn't show a strong positive correlation as a risk factor. However, increasing pack years demonstrated an increased risk. Hypertension, obesity and occupational chemical exposure were shown to increase the risk as found in the west. Other factors such as analgesics, alcohol and social class did not demonstrate a significant correlation.

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Introduction

Renal cell carcinoma (RCC) which commonly originates from proximal renal tubular epithelium accounts for approximately 3% all cancers of adults and 85% of all primary malignant tumours of the kidney (1). It is characterized by a lack of early warning signs, diverse clinical manifestations, and resistance to radiation and chemotherapy.

While the prognosis for localized tumours is good with a five year survival of 88-100% the outcome for metastatic tumour is poor (5 year survival less than 20%).

The risk factors which are studied in the west and rest of the world literature includes its genetic predisposition, tobacco usage, hypertension, obesity and occupational exposures to carcinogens such as heavy metals, petroleum products and asbestos. Contribution of analgesics, diuretics, anti hypertensive agents, renal calculi, and urinary tract infections has been studied with a rather inconclusive outcome. The risk factors for RCC are largely unknown in the third world. As there are hardly any published data on this subject in south Asia this study was designed to test the validity of these findings in this region.

Materials and methods

This study was designed as a matched case control study. A case was defined as a patient with proven RCC, who was treated at one urology unit of a tertiary referral center, between January 1999 and January 2005. Sixty two patients were identified from hospital records. These patients were invited to participate in a clinic where required information was gathered. Among all eligible patients 26 were excluded due to unavailability of reliable data or non response after two rounds of postal communications. Thus 58% (36 of 62) of all eligible patients were interviewed. There was no significant demographic difference between the recruited group and those who failed to participate in the study. For example in the recruited group 77.8 were males and the mean age at diagnosis was 56.9 years (27-83years). Corresponding figures for non-participants were 73% and 58.9 years (33-75). For each participant a control was matched for sex and age (within 5 years) who was followed up in general surgical out patient clinics following a major surgical procedure. Patients with a history of renal tumours and conditions that are directly known to be associated with RCC (eg. Von Hippel Lindau syndrome) and whose presenting complaint was a risk factor under investigation (eg. chronic anlgisic consumption) were excluded from the control group. In person structured interviews were conducted to gather information regarding, demographic data (including social class), smoking habits (number of pack years), hypertension, life time chemical occupational exposure, long term use of analgesics and the body mass index.

Data were analysed with standard matched pair methods. Conditional logistic regression models were used to examine the univariate and multivariate relationships of RCC with various risk factors. The associations were measured by the odds ratios (OR) and their corresponding 95% confidence intervals (95% CI). *p* value less than 0.05 was considered significant and the factors, which were found to be significant in the univariate analysis, were incorporated into the multivariate analysis to detect the confounding effects.

Results

There were 28 (77.8%) male and 08 (22.2%) female patients. The mean age at the diagnosis was 56.92 years (range 27-83). Results are tabulated as follows.

Table 1. Effect of total and current smoking status on RCC (Results of univariate analysis)

Pack years	Cases	Controls	OR	95% CI
0	12	34	1.00	
< 20	12	32	1.06	0.4 - 02.7
20 - 39.9	3	2	4.25	0.2 - 04.2
≥ 40	3	1	8.50	0.8 - 72.3
Non-smoker	13 (36.1%)	34 (47.2%)	1.00	
Former smoker	16 (44.4%)	25 (34.7%)	1.67	
Current smoker	07 (19.4%)	13 (18.1%)	1.41	
Total	36 (100%)	72 (100%)		

Table 2. Effect of duration of hypertension on RCC

Duration of hypertension	*p* value	OR	95% CI
No hypertension		1.0	
Less than 5 years	0.047	3.68	1.02 - 13.36
5 years or more	0.019	6.20	1.34 - 28.66

Table 3. Effect of hypertension and BMI on renal cell carcinoma (Results of the univariate analysis)

	Case	Controls	OR	95% CI
Hypertension	15	14	2.96	1.2-19.4
BMI category (kg/m^2)				
<25	22 (61.1%)	57 (79.2%)	1.0	
25 - 29.9	09 (25.0%)	13 (18.1%)	1.79	0.67 - 4.78
≥30	05 (13.9%)	02 (02.3%)	6.48	1.17 - 35.90
Total	36 (100%)	72 (100%)		

Table 4. Risk factors for renal cell carcinoma (Results of multivariate analysis)

Risk factor	*P* value	OR	95% CI
Hypertension	0.036	4.10	1.09 - 15.36
Occupational exposure	0.019	3.21	1.21 - 08.51
BMI 25 - 30kg/m^2	0.415	1.59	0.52 - 04.87
> 30kg/m^2	0.037	7.42	1.13 - 48.74

Table 5. Distribution of other risk factors between renal cell carcinoma cases and controls

Risk factors	Cases	Controls	OR	95% CI
Occupational exposure +	16	17	2.59	1.2-6.2
Paracetamol (regular use)	09	17	1.08	0.997-9.89
Aspirin (regular use)	08	06	3.14	0.997-9.89

Discussion

In the west the age-adjusted incidence of renal cell carcinoma has been rising by 3% per year. Approximately 31,200 new cases of renal cell carcinoma were diagnosed in the year 2000, and more than 11,900 affected individuals died. Number of deaths worldwide from kidney cancer was expected to exceed 100,000 in the year 2001(2,3). Renal cell carcinoma which is twice as common in male and appears in the fourth to sixth decades, is the sixth leading cause of cancer deaths. Compared to these figures this is a relatively rare cancer in Sri Lanka.

Risk factors

Smoking

Epidemiological studies done in the west in early seventies have identified tobacco exposure as the most widely accepted environmental risk factor although the relative associated risk has been modest ranging from 1.4 to 2.5 compared to controls (4). Ex smokers and current smokers both carried a statically significant high risk than non smokers with an increased relative risk proportionate to the amount and duration of smoking (5). The risk was inversely proportionate to the time elapsed since abstinence and age of

starting to smoke. Industrial exposure to cadmium has been shown to aggravate the risk of developing renal cell carcinoma among smokers. A particularly high risk is reported in smokers who also chew tobacco. Studies have also suggested that in women this may not be as important a risk factor (6, 7). Passive smoking was shown to increase the risk of renal cell carcinoma by 5.7 folds. In the present study associated risk has been modest, ranging from 1.4 to 2.5 compared with controls. When the amount of smoking was considered, in the univariate analysis there was an increasing trend in the odds ratio with increasing pack years of smoking, but this was not statistically significant (Table 6). Risk is directly related to duration of smoking and drop after cessation. Current smoking status was not shown to be significantly associated with RCC in the multivariate analysis (Table 7). Thus the current study failed to show a strong positive relationship as found in western literature.

Hypertension

Hypothesis regarding the connection between hypertension and obesity as high risk predisposing factors for renal cell carcinoma was tested in few studies (8, 9). Postulated pathological process was hypertension lead to renal glomerulosclerosis and tubular interstitial cell proliferation. Diuretics used as medication for hypertension were initially thought to be an independent risk factor but later found to be not so.

In the current study hypertension is an independent risk factor for the development of renal cell carcinoma (OR 4.1, 95% CI 1.09- 15.36) (Table 3).

Because advanced renal disease can lead to hypertension we analysed the duration of hypertension and risk of RCC. The risk of RCC increases with the duration of hypertension (Table 4).

This was in keeping with the results observed in other cohort studies (10). Association between hypertension and renal cell carcinoma is unlikely to be due to consequences of renal cancer as subjects who were diagnosed to have hypertension for more than 5 years have clearly show an increased risk of renal cell carcinoma.

Obesity and body mass index

The majority (61.1%) of the patient population has a BMI less than 25 kg/m^2 (Table 1). However, obesity was identified as a statistically significant risk factor for renal cell carcinoma. A person with a BMI of 30 kg/m^2 has a 6 times increased risk of RCC when compared to a person with a BMI of 25 kg/m^2 or less (OR=6.48, CI=1.17-35.9) (Table 2). The results were similar after making adjustments for potentially confounding effects of other risk factors, i.e. smoking, hypertension, occupational exposure (OR=7.4, CI=1.1-48.7) (Table 3). High risk for renal cell carcinoma with increasing body mass has been noticed by number of observers (11,12). However, definition of obesity has been an inconsistent factor and most were not case controlled studies.

Current study identifies obesity as an independent risk factor for renal cell carcinoma, although majority of the cases were not obese (13).

Prenatal growth and intrauterine development of organs are interconnected and suggested to have an impact on future cancer risk of many organs. Relationship between high birth weight (>3500g) which represent intrauterine growth and increased risk of renal cell carcinoma has been demonstrated (14).

Links between diet and renal cell carcinoma is under investigation. A Swedish study of over 45000 women has failed to demonstrate any association with healthy or western diet with risk of renal cell carcinoma. High risk diets (high protein and fat) and dietary habits have been identified by some studies (15).

Contradictory results have been found in studies regarding the connection between alcohol and renal cell carcinoma risk. While a prospective Finnish study suggest moderate alcohol consumption is connected with decreased risk many other studies demonstrate opposite results (7, 16).

Industrial exposure

There is very limited knowledge about the role of industrial and workplace exposure on the risk of developing renal cell carcinoma. A population study in Canada has demonstrated an excess risk among printers, nursery workers (gardeners), aircraft mechanics, farmers, horticulturists, defense services, wholesale trade, retail trade and exposure to chromium, inorganic acid solutions, rubber, ozone, hydrogen sulphide, ultraviolet irradiation and birth weight (15,16,17). The distribution of positive occupational exposures were shown in Table 5. Positive occupational exposure was shown to increase the risk of RCC by 3.2 folds (95% CI = 1.21- 8.51) in the multivariate analysis. Exposure to petroleum, iron, steel, asbestos, cadmium, textile dyes, dry cleaning solvents and agrochemicals were considered as positive occupational exposure. We also inquired into long term exposure to any other chemicals and we observed that exposure history fertilizer is significantly high among the patients with RCC as compared to controls. Small sample size limits the individual identification of the high risk occupations.

Conclusion

Comparing to the results of western studies, present smoking state didn't show a strong positive correlation as a risk factor. However, increasing pack years demonstrated an increased risk. Occupational exposure, hypertension and relative obesity were shown to increase the risk of renal cell carcinoma. Most of the other less established risk factors did not show any significant association. Present study emphasizes the need of larger scale studies in this direction especially regarding the involvement of industrial carcinogenesis of RCC in this part of the world.

Annex:

Definitions

- Body mass index (BMI) : Weight (kg) / Height (m^2).
- Obesity : BMI more than or equals to 30 kg/m^2.
- Pack year : One pack year = 20 cigarettes smoked per day, for one year.
- Hypertension : Systolic blood pressure more than or equals to 140 mmHg. Diastolic blood pressure more than or equals to 90 mmHg.
- Regular use of paracetamol and aspirin – daily over one year.
- Alcohol consumption – Regular drinker over 5 years.

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