ASSOCIATION OF SMOKING STATUS, TYPE OF CIGARETTES AND OBESITY AS RISK FACTORS AMONG RENAL CELL CARCINOMA HISTOLOGICAL SUBTYPES

[1]Sawkar Vijay Pramod, Faris El Haq, Ferry Safriadi.

[1] Department of Urology, Faculty of Medicine/University of Padjadjaran, Hasan Sadikin Academic Medical Centere, Bandung.

ABSTRACT

Objective: TThis study aims to know the relationship between smoking and obesity as a risk factor among renal cell carcinoma histological subtypes. Material & Methods: This was a retrospective case-control study, with 67 patients with Renal Cell Carcinoma (RCC) at the Department of Urology, Hasan Sadikin Academic Medical Center Bandung from January 2012 to December 2021 as the case group, and 13 patients with benign tumors as the control group. The odds ratio and its significance were calculated. Results: In clear cell RCC, smokers (p-value=0.008), showed strong relationship to cigarette types (p-value=0.013), and obesity (p-value=0.042). In papillary RCC, smokers (p-value=0.035) showed a strong relationship to cigarette types (p-value=0.041). Cloves have a higher risk compared to filtered cigarettes (OR 2.25, 95% CI [0.54-9.25]). Conclusion: Clear cell RCC is most prevalent in smokers. Obesity is associated with clear cell RCC. Cloves pose the greatest risk of clear cell and papillary RCC.

Keywords: Obesity, RCC, smoking, cigarette.

ABSTRAK

Tujuan: Penelitian ini bertujuan untuk mengetahui hubungan antara merokok dan obesitas sebagai faktor risiko pada subtipe histologi karsinoma sel ginjal. Bahan & Cara: Penelitian ini adalah studi kasus-kontrol retrospektif, dengan 67 pasien Renal Cell Carcinoma (RCC) di Departemen Urologi, Hasan Sadikin Academic Medical Center Bandung dari Januari 2012 hingga Desember 2021 sebagai kelompok kasus, dan 13 pasien dengan tumor jinak sebagai kelompok kontrol. Odds ratio dan signifikansinya dihitung. Hasil: Pada clear cell RCC, perokok (p-value=0.008) menunjukkan hubungan yang kuat dengan jenis rokok (p-value=0.013) dan obesitas (p-value=0.042). Pada RCC papiler, perokok (p-value=0.035) menunjukkan hubungan yang kuat dengan jenis rokok (p-value=0,041). Cengkeh memiliki risiko lebih tinggi dibandingkan dengan rokok filter (OR 2.25, 95% CI [0.54-9.25]). Simpulan: Clear cell RCC paling banyak terjadi pada perokok. Obesitas dikaitkan dengan clear cell RCC. Cengkih menimbulkan risiko terbesar dari clear cell RCC dan RCC papiler.

Kata kunci: Obesitas, RCC, merokok, rokok.

Correspondence: Sawkar Vijay Pramod, c/o: Department of Urology, Faculty of Medicine/Hasan Sadikin Academic Medical Center, University of Padjadjaran, Indonesia. Jl. Pasteur No.38 Bandung. Email: doktervj@yahoo.co.id.

INTRODUCTION

Renal cell carcinoma (RCC) accounts for most kidney cancer diagnoses and consists of many subtypes of cancer.[1] The most common subtypes are clear cell subtype (75%), papillary (15%), and chromophobe (5%).[2] Data from the Global Cancer Observatory (GLOBOCAN) Indonesia in 2020, showed the incidence of renal cell carcinoma is 2.25 per 100.000 population with a mortality of 0.58%.[1]

According to Riskesdas 2018, male smokers aged >15 years in Indonesia reached 62.9% of all smokers, becoming the highest age prevalence in the world.[3] This is worrying because smoking is a risk factor for many types of cancer, including RCC.

Meanwhile, obesity is expected to become a global public health concern and a serious problem in developing countries.[4] A strong correlation in terms of carcinogenesis has been recognized, leading to obesity becoming one of the established and modifiable risk factors of RCC.[5]

The prevalence of smoking and obesity in Indonesia is still high, it is still a culture and still common in Indonesia as well as a lack of

understanding and related research about the relationship between smoking status, type of cigarette, and obesity as a risk factor for the histological subtype of RCC.

The link between smoking and kidney cancer, specifically renal cell carcinoma (RCC), has been extensively researched and established. However, it is important to note that RCC can present itself in various subtypes, and the potential correlation between these subtypes and smoking requires further investigation. As such, continued research is necessary to fully understand the complex relationship between smoking and RCC subtypes.

OBJECTIVE

This study aims to know the relationship between smoking and obesity as a risk factor among renal cell carcinoma histological subtypes.

MATERIAL & METHODS

This study is a case-control study by taking secondary data from the Kidney Cancer Database of patients who underwent biopsy, partial and radical nephrectomy at the Department of Urology Hasan Sadikin, Academic Medical Center Bandung. The research subjects were patients with Renal Cell Carcinoma (RCC) at the Department of Urology, Hasan Sadikin Academic Medical Center Bandung from January 2012 to December 2021 who met the inclusion criteria. The subjects of the study were patients with RCC with a total sample of 67 patients using non-probability and purposive sampling methods and 13 patients with benign tumor as a control group. Subtype-specific odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using logistic regression. This research was conducted by researchers independently.

The inclusion criteria in this study were: Patients with RCC based on clinical, histological, laboratory, and radiological diagnoses at the Department of Urology, Hasan Sadikin Academic Medical Center Bandung, and patients who are willing to be included in the study. Exclusion criteria in this study are RCC patients who have a family history of RCC sufferers, patients whose medical record data is incomplete, and patients with urothelial carcinoma.

The patient's smoking history was classified into 4 groups. Group 1 (K1) was a group of patients who did not smoke. Group 2 (K2) is a group of patients who smoked <20 cigarettes/day for ≤ 30 years. Patients who smoked for 31 – 40 years or smoke > 20 cigarettes/day for ≤ 30 years in group 3 (K3). Then patients who smoked in any amount for >40 years were included in group 4 (K4). Based on the type of cigarette consumed by the patient, it is divided into cloves and filters. The subtype of renal tumor histology is classified according to WHO criteria. The obesity classification is divided based on Asia-Pacific criteria. In this study, patients were grouped into the obese class as BMI ≥ 25 and non-obese class as BMI <25.

To determine the homogeneity of the data, a normality test Kolmogorov-Smirnov was carried out. The data were normally distributed if P>0.05. To compare characteristics of sex, and age, using chi-square or ANOVA according to the data category. The test is used to compare smoking status, BMI, and histological type of RCC using the chi-square test and if it does not meet the chi-square requirements, then the cells are combined, and then the Kolmogorov-Smirnov test is performed.

RESULTS

The demographic of the patients based on smoking status and type of cigarettes are summarized in figure 1. The proportion of age and smoking duration of the patients in each subtype of renal cell carcinoma group in this study was summarized in table 1. Statistical test in the clear cell RCC group revealed that the p-value of the smoking status, type of cigarettes, and BMI variable were <0.05 (p=0.008; p=0.013; p=0.042) as shown in table 2, which indicates there is a statistically significant difference in proportion between smoking status, type of cigarettes, and obesity to the clear cell carcinoma number.

The smoking status and type of cigarettes of the papillary RCC group are statistically significant in comparison to the clear cell RCC group, with p-value=0.035 and 0.041, respectively. The p-value for smoking status, type of cigarettes, and BMI in the chromophobe cell cancer patient group was >0.05 which indicates statistical significance.
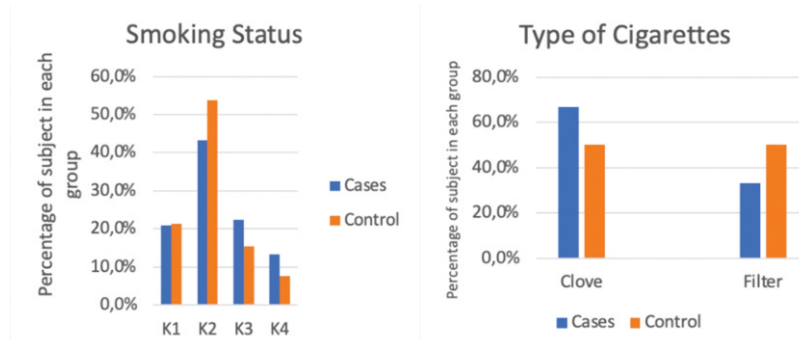
Figure 1. Demographic of the patients based on smoking status and type of cigarettes.

Table 1. Proportion based on age and smoking duration in renal cell carcinoma.

Variable	Control (n=13)	Case			
		Clear cell RCC (n=49)	Papillary RCC (n=10)	Chromophobe RCC (n=8)	Total RCC (N=67)
Age					
Mean ± Std	49.92±15.553	54.88±10.700	55.90±12.476	50.50±14.570	54.51±11.373
Median	52.00	55.00	54.50	51.50	55.00
Range (min-max)	20.00-70.00	23.00-85.00	34.00-71.00	31.00-69.00	28.00-85.00
Smoking Duration					
Mean±Std	18.31±13.714	24.33±14.917	23.20±13.935	21.88±14.999	23.87±14.590
Median	22.00	27.00	26.00	25.00	27.00
Range (min-max)	0.00-36.00	0.00-47.00	0.00-41.00	0.00-42.00	0.00-47.00

Notes: Categorical data is presented with number/frequency and percentage, while numerical data is presented with mean, median, standard deviation and range. RCC: Renal Cell Carcinoma.

Table 2. Smoking status, type of cigarettes, and bmi as risk factor of all-type renal cell carcinoma.

Variable	Controls (n=13)	Clear Cell RCC			Papillary RCC			Chromophobe RCC		
		Cases (n=49)	OR (CI)	P	Cases (n=10)	OR (CI)	P	Cases (n=8)	OR (CI)	P
Smoking Status										
K1	3 (23.1%)	10 (20.4%)		0.008*	2 (20%)		0.035*	2 (25%)		0.622
K2	7 (53.8%)	20(40.8%)			5 (50%)			4 (50%)		
K3	2 (15.4%)	12 (24.5%)			2 (20%)			1(15.4%)		
K4	1 (7.7%)	7 (14.3%)			1 (10%)			1 (7.7%)		
Type of Cigarettes										
Clove	5 (50%)	27 (69.2%)		0.013*	4(57.1%)		0.041*	3 (60%)		0.748
Filter	5 (50%)	12 (30.8%)			3(42.9%)			2 (40%)		
BMI										
Obese	9 (69.2%)	35 (71.4%)	2.312	0.042*	7 (70%)	1.748	0.393	5(62.5%)	0.617	0.371
Non Obese	14 (28.6%)	14 (28.6%)			3 (30%)			3(37.5%)		

Table 3. Subtype analysis of type of cigarettes in renal cell carcinoma.

Variable	Controls (n=13)	Clear Cell RCC			Papillary RCC			Chromophobe RCC		
		Cases (n=49)	OR (CI)	P	Cases (n=10)	OR (CI)	P	Cases (n=8)	OR (CI)	P
Type of Cigarettes			2.25 (0.54-9.25)	0.013*		1.33 (0.19-9.31)	0.041*		1.5 (0.17-13.22)	0.748
Clove	5 (50%)	27 (69.2%)			4(57.1%)			3 (60%)		
Filter	5 (50%)	12 (30.8%)			3(42.9%)			2 (40%)		

103

DISCUSSION

According to van Osch et al meta-analysis, smoking is one of the most modifiable kidney cancer risk factors. It also states current and former smokers have a 3.14 and 2.53 times greater risk of developing kidney cancer than non-smokers, respectively. This risk grows steadily with higher cigarette consumption with >15 cigarettes per day or 50 packs per year.[6] The findings of this study are consistent with those of previous studies.

There's a paucity of research on the effect of cigarette brands on renal cancer subtypes. A study by Patel et al. showed clear cell and papillary RCC subtypes were the most prevalent, while chromophobe RCC was the least prevalent.[7] This is congruent with the current study, which found that participants with clear cell RCC were the most prevalent and those with chromophobe RCC were the least prevalent. Long-term smoking (>30 years) was more strongly linked to clear cell RCC compared to other kinds. Local hypoxia and oxidative stress processes induced by smoking are responsible for the greater prevalence of clear cell RCC and papillary RCC.[8]

An in vitro study conducted by Shin et al. in vitro toxicity study was comparing the toxicity of filtered and non-filtered cigarettes, which showed the total particulate matter (TPM) was reduced by up to 45 percent in filter cigarettes compared to non-filtered cigarettes. The significant consequence of using a carbon filter is a reduction in TPM caused by a decrease in the amount of tar inhaled as a result of filtration.[9-10] This suggests that the use of a filter reduces the number of carcinogenic chemicals in filtered cigarettes. This explains the higher odds ratio (OR=2.25, 95% CI [0.54-9.25]) of clove cigarettes found in this study.

A prior study stated that current smokers had a worse prognosis in terms of overall mortality (OM), disease-specific mortality (DSM), overall survival (OS), cancer-specific survival (CSS), and progression-free survival (PFS).[11] This study is anticipated to aid in predicting the histologic subtype of kidney cancers based on risk factors, particularly smoking. When a biopsy is not possible or when the histologic results are ambiguous, this factor may be considered for patients.

We also discovered that obesity is related to the clear cell RCC subtype. This result is coherent with a previous study that showed obesity was related to clear cell RCC and chromophobe RCC, but not to papillary RCC. However, the prior study was unable to specify how exactly weight contributes to the development of chromophobe. Obesity probably affects TERT expression and mitochondrial function, which are frequently dysregulated in chromophobe RCC.[12] Another study supports the hypothesis is stated that excess weight correlates with clear cell RCC and that increased BMI appeared to be independently related to the clear-cell variation in their case-control analysis. They discovered that for every 1 kg/m^2 increase in BMI, the likelihood of having clear cell RCC as a subtype increased by 4%. They propose several mechanisms for the development of clear cell RCC, including elevated estrogen levels in obese patients that may contribute to tumor genesis, association with impaired immune function, and the presence of negative regulators of T cell activation on clear-cell RCC.[13]

CONCLUSION

The clear cell RCC is the most common subtype in smokers, while the chromophobe RCC is the least common. Clove cigarettes and more intense smoking can increase the risk of clear cell RCC and papillary RCC, but not chromophobe RCC. Obesity was found to have a significant relationship with clear cell RCC.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May; 71(3): 209–49.
2. Cheville JC, Lohse CM, Zincke H, Weaver AL, Blute ML. Comparisons of Outcome and Prognostic Features Among Histologic Subtypes of Renal Cell Carcinoma. Am J Surg Pathol. 2003; 27(5): 612-24.
3. Umbas R, Safriadi F, Mochtar CA, Djatisoesanto W, Rizal A, Hamid AH. Urologic cancer in Indonesia. Jpn J Clin Oncol. 2015; 45(8): 708-12.
4. Obesity and central obesity in Indonesia: evidence from a national health survey. Med J Indones. 2018; 27(2): 114-20.
5. Aurilio G, Piva F, Santoni M, Cimadamore A, Sorgentoni G, Lopez-Beltran A, et al. The role of obesity in renal cell carcinoma patients: Clinical-pathological implications. Int J Mol Sci. 2019 Nov 1; 20(22).
6. Van Osch FHM, Jochems SHJ, Schooten FJ van, Bryan RT, Zeegers MP. Quantified relations between

exposure to tobacco smoking and bladder cancer risk: a meta-analysis of 89 observational studies. Int J Epidemiol. 2016; 45(3): 857–70.

7. Patel NH, Attwood KM, Hanzly M, Creighton TT, Mehedint DC, Schwaab T, et al. Comparative Analysis of Smoking as a Risk Factor among Renal Cell Carcinoma Histological Subtypes. J Urol. 2015; 194(3): 640–6.

8. Yeboah MM, Xue X, Duan B, Ochani M, Tracey KJ, Susin M, et al. Cholinergic agonists attenuate renal ischemia–reperfusion injury in rats. Kidney Int. 2008; 74(1): 62.

9. Shin HJ, Sohn HO, Han JH, Park CH, Lee HS, Lee DW, et al. Effect of cigarette filters on the chemical composition and in vitro biological activity of cigarette mainstream smoke. Food Chem Toxicol. 2009; 47(1): 192–7.

10. Ito H, Matsuo K, Tanaka H, Koestler DC, Ombao H, Fulton J, et al. Nonfilter and filter cigarette consumption and the incidence of lung cancer by histological type in Japan and the United States: analysis of 30-year data from population-based cancer registries. Int J Cancer. 2011; 128(8): 1918–28.

11. 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(1): 101–8.

12. Callahan CL, Hofmann JN, Corley DA, Zhao WK, Shuch B, Chow WH, et al. Obesity and renal cell carcinoma risk by histologic subtype: a nested case-control study and meta-analysis. Cancer Epidemiol. 2018; 56: 31.

13. Lowrance WT, Thompson RH, Yee DS, Kaag M, Donat SMH, Russo P. Obesity is associated with a higher risk of clear-cell renal cell carcinoma than with other histologies. BJU Int. 2010 Jan; 105(1): 16–20.