Comparative Analysis of Smoking as a Risk Factor among Renal Cell Carcinoma Histological Subtypes

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Abbreviations and Acronyms

BMI = body mass index

ccRCC = clear cell renal cell carcinoma

chRCC = chromophobe renal cell carcinoma

mpy = mean pack-years

ppd = packs per day

pRCC = papillary renal cell carcinoma

RCC = renal cell carcinoma

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Purpose: Smoking is the best established modifiable risk factor for renal cell carcinoma. However, the risks of individual renal cell carcinoma histological subtypes are unknown. Therefore, we investigated the relationship between smoking and renal cell carcinoma subtype.

Materials and Methods: Cigarette smoking data were prospectively collected from 816 consecutive patients with nonfamilial renal cell carcinoma (705) or benign pathology (111) undergoing nephrectomy at a single National Comprehensive Cancer Network® cancer center, and were retrospectively tested for an association with histological diagnosis on univariable and propensity adjusted analyses.

Results: Smoking was reported by 51% of patients, including 21% active smokers and 30% former smokers. Active smoking was more common with clear cell (23%) or papillary (26%) renal cell carcinoma than benign histology (14%, $p < 0.05$ each), yet strikingly less common with chromophobe renal cell carcinoma (6%, $p < 0.05$ vs clear cell or papillary). Any smoking history (active or former) was also relatively uncommon with chromophobe (26%) vs clear cell (53%, $p = 0.003$) or papillary (58%, $p = 0.001$) histology. Smoking extent based on mean pack-years was significantly greater with clear cell (15.3 mean pack-years) or papillary (15.2 mean pack-years) renal cell carcinoma but not chromophobe renal cell carcinoma (9.4 mean pack-years) compared to benign histology (9.4 mean pack-years, $p \leq 0.05$, $p < 0.05$, $p = 1.0$, respectively). On propensity analyses adjusting for multiple variables, clear cell (OR 2.2, $p < 0.05$) and papillary (OR 2.4, $p < 0.05$) histologies but not chromophobe histology remained independently associated with active smoking.

Conclusions: Traditional understanding of smoking as a renal cell carcinoma risk factor applies to clear cell and papillary renal cell carcinoma but not the chromophobe subtype. These findings underscore distinct carcinogenic mechanisms underlying the various renal cell carcinoma subtypes.

Key Words: smoking; carcinoma, renal cell; histology

Renal cell carcinoma encompasses the majority of kidney cancer diagnoses and is comprised of multiple cancer subtypes, each defined by a distinct histology according to the WHO.[1] The most common subtypes include clear cell (75%), papillary (15%) and chromophobe (5%). RCC subtypes differ in metastatic potential and clinical responsiveness to

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immunotherapeutic or antiangiogenic therapies, and may provide prognostic value for patient counseling.[2] Subtype specific carcinogenic mechanisms are suggested by different characteristic cytogenetic alterations, including chromosome 3p loss for ccRCC, chromosome 7 and 17 gain for pRCC, and multi-chromosomal monosomy for chRCC, and by scarce mutational overlap at the single gene level.[1,3] Distinct carcinogenic mechanisms of RCC subtypes may reflect differences in cell origin as the ccRCC and pRCC subtypes are believed to originate from the proximal renal nephron epithelium as opposed to the distal nephron for chRCC.[4]

While RCC was among the first cancers with histological subtypes formally recognized nearly 2 decades ago, it is still uncertain how RCC risk factors apply to these individual subtypes. Identification of subtype specific risk factors may improve our understanding of carcinogenic mechanisms, thereby leading to more effective prevention and treatment strategies. A large body of epidemiological literature describes risk factors for RCCs overall, including male gender, tobacco use, hypertension and obesity, but without regard to RCC subtype.[5–7] The best established modifiable risk factor for RCC is tobacco use, typically cigarette smoking.[7,8] According to the U.S. Surgeon General there are sufficient data to support causality between smoking and the development of RCC from the known carcinogenic effects of numerous tobacco components.[9] However, the risk of each subtype with smoking has not yet been delineated as epidemiological investigations have generally not considered subtype differences.[6–10]

We investigate the relationship between smoking and the incidence of RCC subtypes in a large cohort of patients undergoing nephrectomy at our institution. Our goal was to determine whether this well established carcinogen contributes similarly to the oncogenesis of all RCC subtypes or has a differential effect. Our findings are novel as they suggest that the classic association between smoking and RCC applies only to certain subtypes, underscoring distinct molecular carcinogenic mechanisms contributing to these heterogeneous cancers.

MATERIALS AND METHODS

Patients

From 1996 to 2013 smoking history was recorded during preoperative consultation for 905 consecutive patients undergoing partial or radical nephrectomy at Roswell Park Cancer Institute, a National Comprehensive Cancer Network cancer center. These smoking data and other clinicopathological data were extracted from a prospectively populated Roswell Park Cancer Institute nephrectomy database under institutional review board approval. Excluded from analysis were 35 patients with urothelial carcinoma, 20 with metastasis to the kidney and 34 with a family history of RCC. The remaining 816 consecutive patients with nonfamilial RCC or benign histopathology were retrospectively studied for an association of cigarette smoking with nephrectomy histology.

Cigarette smoking history was classified as active, former or never for each patient, and secondhand exposure was not included in the analysis. For 739 (91%) patients the total smoking years and average number of packs per day were recorded, enabling the calculation of pack-year use as the product of these 2 variables. Renal tumor histological subtype was classified according to WHO criteria. Patients with rare RCC subtypes (eg collecting duct RCC), unclassified RCC or multiple RCC subtypes (metachronous or synchronous) were analyzed collectively as the category of other RCC. Benign renal histologies included angiomyolipoma, oncocytoma, mixed epithelial stromal tumor, cyst, glomerulosclerosis, interstitial fibrosis and infection.

Statistics

Patient and tumor characteristics were reported as means, medians and standard deviations for continuous variables, and as frequencies and relative frequencies for categorical variables. Mean pack-year use and rates of active or any (including former) smoking were compared among patients according to RCC histological subtype or benign histology. Comparisons between groups were made using the 2-sided Wilcoxon rank sum and Fisher exact tests for continuous and categorical variables, respectively. A propensity adjusted analysis was conducted to compare smoking measures between RCC histological subtypes and benign histology. Using logistic regression, propensity scores were obtained based on age, gender, race, BMI and tumor size. Active smoking rates were evaluated using stratified logistic regression with propensity quintile as the stratification factor. Odds ratios and corresponding Wald confidence intervals were obtained from model estimates, and model fit was assessed using Pearson and deviance residual plots. Mean pack-years, intensity and duration were evaluated using ANCOVA, with the propensity score as the additional covariate. Mean differences were obtained using the least squares means method, and model fit was assessed using quantile-quantile and residual plots about the studentized residuals. All analyses were conducted with SAS® v9.4 at a significance level of 0.05.

RESULTS

A positive smoking history was reported by 414 (50.7%) of patients, including 171 (21.0%) active smokers and 243 (29.8%) former smokers. When stratified according to age less than 40, 40 to 49, 50 to 59, 60 to 69, 70 to 79, and 80 years old or older, active and former smoking rates were 5.9%, 21.1%, 39.8%, 25.2%, 7.6%, 1.0% and 1.7%, 9.5%, 16.9%, 38.3%, 22.2% and 11.5%, respectively. Active smokers were younger and more often African-American than