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Comprehensive Assessment of the Impact of Cigarette Smoking on Survival in Clear Cell Kidney Cancer

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Abstract

Purpose—Despite recent reports describing an association between smoking exposure and kidney cancer stage at diagnosis, the impact of smoking on cancer-specific outcomes is understudied. We evaluated the impact of smoking exposure on cancer-specific death in patients with clear cell renal cell carcinoma (ccRCC) treated with surgery.

Materials and Methods—Patient and disease characteristics from 1,625 patients with nonmetastatic ccRCC treated with partial or radical nephrectomy between 1995 and 2012 were collected from a prospectively maintained database at Memorial Sloan-Kettering Cancer Center. The associations between smoking status and both advanced disease (American Joint Committee on Cancer stage >2) and cancer-specific death were determined.

Results—The prevalence rates of current, former, and never smoking at diagnosis were 16%, 30%, and 54%, respectively, and 62.4% of patients reported a 20 pack-year smoking history. With a median follow-up period among survivors of 4.5 years (IQR 2.2–7.9), 19.5% (n=316) died during follow-up, 108 (34%) due to disease. We demonstrated 20 pack-year smoking history was associated with a significantly increased risk for advanced disease (American Joint Committee on Cancer stage > 2) on logistic regression (odds ratio 1.43, 95% confidence interval 1.02–2.00). Although pathologic stage and Fuhrman grade adversely affected the likelihood of cancer-specific death, smoking status was not associated with cancer-specific death in multivariable competing

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Contribution:

All authors (BE, HF, ECZ, AAH, PR) have contributed equally to the study design, conduct of the study, data collection, data analysis, and manuscript preparation.

Attestation:

All authors attest to approving the final manuscript. BE, ECZ, and PR have reviewed the original study data and data analysis, and attest to the integrity of the original data and the analysis reported in this manuscript. BE and ECZ are the archival authors who are responsible for maintaining the study records.

IRB:

The data used in this study were reviewed by the institutional review board and granted a Waiver of Authorization determined to be exempt from human subject research consent requirement.

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risks analysis ($p=0.29$). However, current smokers faced a significantly higher risk for death from other causes as compared with never smokers (hazard ratio 1.93, 95% confidence interval 1.29–2.88).

Conclusions—Patients with heavy smoking exposure histories presented with more advanced ccRCC. Although smoking status at diagnosis and cumulative smoking exposure were not associated with ccRCC-specific death, our findings suggest that smoking exposure increases risk for death from other causes in patients with ccRCC. Treatment plans to promote smoking cessation are recommended for these patients.

Keywords

Kidney cancer; smoking; clear cell; renal cell carcinoma; outcomes

Introduction

Kidney cancer accounts for 2% of all incident malignancies worldwide, with 64,770 cases and 13,570 deaths in the United States in 2012.¹ The increased use of cross-sectional imaging has contributed to the increasing detection of incidental renal masses; however, earlier detection has not decreased the risk for kidney cancer mortality.² Most strategies to improve kidney cancer survival have focused on optimizing surgical technique and incorporating targeted therapies for patients with metastatic disease, with less attention given to addressing modifiable risk factors, such as cigarette smoking.³ Despite numerous epidemiologic studies evaluating the etiology of renal cell carcinoma, the risk factors for disease progression are still poorly understood. Cigarette smoking consistently has been shown to be associated with incidental clear cell renal cell carcinoma (ccRCC), and studies that support a causal relationship note a clear dose–response correlation and an observed benefit of smoking cessation on risk.^{4,5}

Recently, a study of men with kidney cancer treated with nephrectomy suggested that smoking may be associated with an increased risk for cancer-specific mortality. Moreover, heavy smoking was independently associated with advanced pathologic disease, indicating that cigarette smoking affects renal cell carcinogenesis and promotes disease progression.⁶ Similarly, further investigation of molecular data in another retrospective study demonstrated that a history of smoking was associated with increased risk for having mutated *p53* and worse cancer-specific survival after surgery.⁷ These studies were limited in some cases by insufficient sample size to evaluate the impact of smoking on survival outcome or failed to quantify the intensity of smoking, including cigarettes per day and years of smoking. Furthermore, kidney cancer is composed of a heterogeneous class of tumors that arise from several cell types within the nephron and exhibit distinctive natural histories. Previous studies combined all histologic subtypes together, which may obscure the risk of cigarette smoking, especially considering the association between smoking and kidney cancer is primarily established for ccRCC.

In the present study, we examined the impact of smoking status and cumulative smoking exposure on the risk for cancer-specific death among 1,625 patients with ccRCC treated with partial or radical nephrectomy at a single high-volume cancer center.

MATERIALS AND METHODS

Patient Selection

Data on 3,155 consecutive patients with renal cell carcinoma who underwent partial or radical nephrectomy between 1995 and 2012 were obtained from a prospectively maintained clinical database. Genitourinary surgeons performed radical nephrectomy according to standard protocol, which involves excision of the kidney along with Gerota's fascia. Similarly, partial nephrectomy was performed by excising the tumor and adjacent normal parenchyma. The hilar and regional lymph nodes adjacent to the ipsilateral great vessels were resected as needed, along with enlarged lymph nodes that were either identified on preoperative CT scans or palpable intraoperatively. The institutional review board approved the request for exemption of this retrospective study and approved waivers for Health Insurance Portability and Accountability Act authorization and informed consent. Patients were excluded if they experienced an operative death (n=4), had non-ccRCC histology (n=1,004), had incomplete smoking history data (n=512), or presented with metastatic disease (n=10), resulting in a total sample size of 1,625.

Pathologic Evaluation

Surgical specimens were processed using standard pathologic techniques and were reviewed by experienced genitourinary pathologists. All specimens were histologically confirmed to be ccRCC. Tumors were staged according to the 2007 American Joint Committee on Cancer (AJCC) TNM classification.⁸ Tumor grading followed the Fuhrman system.⁹

Follow-up Regimen

Patients were seen 1 month after surgery, then every 6 months for the first 2 years, and annually thereafter. Follow-up consisted of history, physical examination, serum chemistry studies, chest radiography, and renal ultrasound. The follow-up regimen was personalized based on pathologic characteristics and surgical technique. The cause of death was determined by chart review, corroborated by death certificates, and agreed on by an interdisciplinary conference.

Smoking Exposure

Self-reported smoking data were routinely collected on all patients at the time of diagnosis. Available variables for analysis included smoking status (current, former, or never smoker), duration of smoking (<20, 20–39, and ≥40 years), and quantity smoked (1–10, 11–20, 21–30, and >30 cigarettes per day). Smoking status was determined at the time of diagnosis, and current smokers were defined as active smokers or having stopped within 1 year of diagnosis. Patients were identified as former smokers if they had stopped smoking at least 1 year before diagnosis, based on previously published definitions.¹⁰ Duration of smoking and number of cigarettes per day were used to derive pack-years smoked (<20 vs ≥20 pack-years) as a measure of cumulative smoking exposure for all former and current smokers.

Statistical Analysis

Descriptive statistics were calculated for demographic, disease, and smoking characteristics. Associations between categorical variables were assessed using the chi-square test, whereas the Kruskal-Wallis test was used for continuous variables. Follow-up time was calculated from the date of diagnosis. Because smoking is an established risk factor for common health problems that increase risk for death, we conducted competing risks analyses. The cumulative incidence was estimated, where cancer-specific death was the primary event of interest and death from other causes was treated as a competing event. Gray's test was used to determine differences in cumulative incidence function between groups.¹¹ Multivariable competing risks regression models were adjusted for traditional prognostic factors that were identified a priori and included age at diagnosis, sex, American Society of Anesthesiologists score, pathologic stage, and Fuhrman grade. In addition, univariable logistic regression was used to determine patient characteristics associated with increased risk for advanced disease defined as AJCC stage > 2. Statistical significance was defined as $p < 0.05$. Statistical analyses were conducted using SAS (version 9.2, 2008; SAS Institute, Cary, NC) and R (version 2.11.0, 2010; R Development Core Team), including the 'survival' and 'cmprsk' packages.

RESULTS

Table 1 shows the associations between demographic and pathologic characteristics by smoking status. The patient population was 91.1% white and 65.6% male, with a median (IQR) age at diagnosis of 60.9 (51.8–70) years. Seventy-four percent of patients had localized disease based on pathologic tumor stage (pT ≤ T2), and 1% had lymph node metastases. Sixteen percent of patients were current smokers at the time of diagnosis, and 30% were former smokers. Among ever smokers, 73.3% smoked for ≥ 20 pack-years. Compared with never and former smokers, current smokers were significantly more likely to be younger and male (all $p < 0.05$).

The median (IQR) follow-up time for patients was 4.5 (2.2–7.9) years. During the follow-up period, 19% ($n=316$) of the study population died. Of these deaths, 34% ($n=108$) were attributable to metastatic RCC, 57% ($n=181$) were due to other causes, and 9% ($n=27$) resulted from an unknown cause.

Table 2 shows the results of logistic regression analyses evaluating the association between individual smoking characteristics and advanced disease. In patients with ≥ 20 pack-year smoking histories, there was a significantly increased risk for advanced disease (AJCC stage > 2). However, the association between heavy smoking and advanced disease was not found consistently across smoking characteristics, including smoking status and years since cessation. Figure 1 presents survival probabilities by smoking status. Smoking status was not significantly associated with kidney cancer mortality ($p=0.057$) on univariable analysis, nor was pack-years ($p=0.26$). However, heavy smoking (≥ 20 pack-years) was associated with a significantly increased risk for death from other causes ($p=0.001$). Although pathologic stage and Fuhrman grade adversely affected cancer-specific survival, smoking status was not associated with cancer-specific death in multivariable competing risks analysis ($p=0.29$). However, current smokers faced a significantly higher risk for death from

other causes as compared with never smokers (hazard ratio 1.77, 95% confidence interval 1.23–2.44).

DISCUSSION

Cigarette smoking remains a highly prevalent habit in the United States. The Centers for Disease Control and Prevention report that 21% of U.S. adults are active smokers, and 21% describe themselves as former smokers.¹² Cigarette smoking is the most consistent modifiable risk factor for ccRCC; however, the impact of smoking on survival in patients with ccRCC remains understudied. Our objective was to report the most comprehensive and detailed study evaluating the risk of smoking exposure on ccRCC pathologic stage and survival outcomes in a large surgical series.

The present findings suggest that smoking status at diagnosis and cumulative smoking exposure do not significantly increase the risk for kidney cancer death; however, our study also highlights the substantial risk for death faced by patients with ccRCC who are current smokers. Importantly, smokers with high-intensity cumulative exposure (≥ 20 pack-years) are at a significantly increased risk for being diagnosed with disease of an advanced pathologic stage. Overall, our study underscores the importance of promoting smoking cessation among patients with kidney cancer.

The mechanism for smoking-induced renal cell carcinogenesis has not been delineated; however, the strongest evidence for a role of individual carcinogens is for polycyclic aromatic hydrocarbons, aromatic amines, heterocyclic aromatic amines, and *N*-nitrosamines. Among the *N*-nitrosamines present in cigarette smoke, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) is the most abundant, the most potent in terms of carcinogenicity, and has been associated with risk for ccRCC in a case-control study.¹³ In another study of 470 sporadic ccRCC cases, von Hippel-Lindau (VHL) inactivation was identified as a biomarker of tumor heterogeneity, and germline alterations of the *VHL* gene were identified in the majority of families with VHL disease. Importantly, smokers had a higher prevalence of tumors without detectable *VHL* sequence alteration or epigenetic inactivation, suggesting that these tumors may be biologically distinct.¹⁴

The results of our study corroborate the biologic gradient effect of cigarette smoking on kidney cancer seen in previous reports that considered the effect of smoking exposure on kidney cancer prognosis. Our data are consistent with a previous study identifying smoking intensity as an independent risk factor for advanced kidney cancer. In that study, Tsivian et al⁶ reviewed half the number of patients as our study (N = 845) and included all histologic subtypes. Despite the small sample size to assess survival outcomes, the authors demonstrated that smoking status, duration, and cumulative exposure (in pack-years) were significantly associated with advanced pathologic stage after surgery.⁶ In a retrospective study evaluating a similar sample size of patients (N = 802), Kroeger et al⁷ were able to demonstrate an independent risk for kidney cancer death in patients with a history of smoking. Unlike the study by Tsivian et al⁶ and our present report, the study by Kroeger et al⁷ considered smoking exposure as a binary variable (nonsmoker or smoker); therefore, the authors did not report findings based on multiple aspects of smoking status, including

cumulative exposure and duration of cessation. Similar to Tsivian et al⁶, Kroeger et al⁷ did not distinguish between the histologic subtypes of kidney cancer.

In our study, we did not find smoking status to be an independent risk factor for kidney cancer-specific mortality. However, we did identify cumulative smoking exposure as an important risk factor for advanced disease, and our data suggest that many smokers with ccRCC treated by surgery may be at increased risk for death from other causes. Unlike previous reports, we used competing risks analyses to examine the cumulative incidence of kidney cancer death because smoking is associated with an increased risk for death from cardiovascular and pulmonary morbidities. Remarkably, approximately half of the patients with ccRCC were current or former smokers. Patients with ccRCC have a high probability of being smokers, and because effective smoking cessation treatments exist for patients with cancer, the promotion of smoking cessation among patients with ccRCC who are current smokers or at increased risk for relapse after recently quitting is warranted.¹⁵

Strengths of the present study include the multiple aspects of smoking status evaluated and an analytical approach that considered competing risks. In addition, ours is the largest study of the impact of smoking on survival in patients with ccRCC for whom detailed smoking data is available. Limitations are acknowledged. Because prospective data on changes in smoking behavior after diagnosis were not available, we considered only smoking status at diagnosis. Recent studies in other malignancies suggest that smoking often shifts after treatment and post-diagnosis smoking may be an important factor to measure.^{16,17} The smoking data were extracted from a prospectively maintained database; however, they are based on self-reporting and are prone to recall bias and intentional false reporting.¹⁸

Despite numerous studies reporting a consistent association between smoking and ccRCC diagnosis, and recent studies, including the present study, demonstrating smoking to be an independent risk for advanced disease, a survey of 1,821 U.S. urologists found that more than half of them never discuss smoking cessation with their patients.¹⁹ The findings of our study initiated a quality initiative at our institution in which we reviewed patient charts in kidney and bladder cancer clinics and discovered less than half of current smokers were referred to smoking cessation programs; however, more than two thirds of patients who were referred did follow up with their appointment. The diagnosis of cancer and discussion of treatment presents an excellent opportunity to encourage smoking cessation among patients.^{20,21} We believe urologists are in a unique position to promote smoking cessation as part of comprehensive clinical care.²²

Conclusion

The prevalence of smoking is high among patients diagnosed with ccRCC, and the majority of patients identified as current smokers at the time of diagnosis report smoking heavily (> 20 pack-years). Patients with heavy smoking exposure presented with more advanced ccRCC compared with former smokers or nonsmokers. Although smoking status at diagnosis and cumulative smoking exposure were not associated with cancer-specific death, our findings suggest that smoking exposure substantially increases risk for death from other

causes in patients with ccRCC. Treatment plans to promote smoking cessation are recommended for these patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AJCC	American Joint Committee on Cancer
ccRCC	clear cell renal cell carcinoma
CI	confidence interval
IQR	interquartile range
VHS	von Hippel-Lindau

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Figure 1.
Cumulative incidence of death by smoking status (left) and pack-years among smokers (right).

Table 1

Characteristics of 1,625 patients with clear cell renal cell carcinoma by smoking status

	Overall (N =1,625)	Never (n=872; 54%)	Former (n=487; 30%)	Current (n=266; 16%)	pValue ^J
Age (years), Median (IQR)	60.9 (51.8–70.0)	60.9 (50.8–70.3)	63.6 (55.8–70.9)	56.6 (48.0–64.9)	<0.001
Sex, n(%)					<0.001
Male	1,066 (65.6)	532 (61.0)	348 (71.5)	186 (69.9)	
Female	559 (34.4)	340 (39.0)	139 (28.5)	80 (30.1)	
Race, n(%)					0.071
White	1,481 (91.1)	779 (89.3)	457 (93.8)	245 (92.1)	
Other	132 (8.1)	86 (9.9)	26 (5.3)	20 (7.5)	
Missing	12 (0.7)	7 (0.8)	4 (0.8)	1 (0.4)	
BMI, n(%)					0.488
<25	301 (18.5)	162 (18.6)	74 (15.2)	65 (24.4)	
25–30	614 (37.8)	336 (38.5)	185 (38.0)	93 (35.0)	
30	691 (42.5)	359 (41.2)	225 (46.2)	107 (40.2)	
Missing	19 (1.2)	15 (1.7)	3 (0.6)	1 (0.4)	
Hypertension, n (%)					<0.001
Yes	883 (54.3)	471 (54.0)	293 (60.2)	119 (44.7)	
No	742 (45.7)	401 (46.0)	194 (39.8)	147 (55.3)	
Diabetes, n (%)					0.437
Yes	258 (15.9)	132 (15.1)	86 (17.7)	40 (15.0)	
No	1367 (84.1)	740 (84.9)	401 (82.3)	226 (85.0)	
ASA score, n (%)					0.007
Healthy	952 (58.6)	538 (61.7)	261 (53.6)	153 (57.5)	
Not healthy	654 (40.2)	322 (36.9)	224 (46.0)	108 (40.6)	
Missing	19 (1.2)	12 (1.4)	2 (0.4)	5 (1.9)	
Presentation, n (%)					0.599
Incidental	1,219 (75.0)	656 (75.2)	367 (75.4)	196 (73.7)	
Local	343 (21.1)	188 (21.6)	100 (20.5)	55 (20.7)	
Systemic	54 (3.3)	25 (2.9)	16 (3.3)	13 (4.9)	

	Overall (N =1,625)	Never (n=872; 54%)	Smoking status Former (n=487; 30%)	Current (n=266; 16%)	pValue ^J
Missing	9 (0.6)	3 (0.3)	4 (0.8)	2 (0.8)	
T stage, n (%)					0.198
T1a	793 (48.8)	441 (50.6)	218 (44.8)	134 (50.4)	
T1b	323 (19.9)	176 (20.2)	101 (20.7)	46 (17.3)	
T2a	61 (3.8)	33 (3.8)	19 (3.9)	9 (3.4)	
T2b	25 (1.5)	12 (1.4)	4 (0.8)	9 (3.4)	
T3a	242 (14.9)	117 (13.4)	85 (17.5)	40 (15.0)	
T3b	168 (10.3)	86 (9.9)	55 (11.3)	27 (10.2)	
T3c	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	
T4	12 (0.7)	7 (0.8)	4 (0.8)	1 (0.4)	
N stage, n (%)					0.014
N0	496 (30.5)	264 (30.3)	171 (35.1)	61 (22.9)	
N1	17 (1.0)	8 (0.9)	5 (1.0)	4 (1.5)	
NX	1112 (68.4)	600 (68.8)	311 (63.9)	201 (75.6)	
AJCC stage, n (%)					0.241
1	1113 (68.5)	616 (70.6)	318 (65.3)	179 (67.3)	
2	83 (5.1)	43 (4.9)	22 (4.5)	18 (6.8)	
3	415 (25.5)	205 (23.5)	143 (29.4)	67 (25.2)	
4	12 (0.7)	7 (0.8)	4 (0.8)	1 (0.4)	
Missing	2 (0.1)	1 (0.1)	0 (0.0)	1 (0.4)	
Grade, n (%)					0.044
1	88 (5.4)	46 (5.3)	21 (4.3)	21 (7.9)	
2	908 (55.9)	512 (58.7)	259 (53.2)	137 (51.5)	
3	527 (32.4)	264 (30.3)	171 (35.1)	92 (34.6)	
4	90 (5.5)	40 (4.6)	34 (7.0)	16 (6.0)	
Missing	12 (0.7)	10 (1.1)	2 (0.4)	0 (0.0)	
Pack-years, n(%)					<0.001
<20	283 (37.6)	NA	212 (43.5)	71 (26.7)	
20	470 (62.4)	NA	275 (56.5)	195 (73.3)	
Years since quitting, n (%)					N/A

	Overall (N =1,625)	Never (n=872; 54%)	Smoking status Former (n=487; 30%)	Current (n=266; 16%)	pValue ^I
<5	41 (8.4)	NA	41 (8.4)	NA	
5-9	59 (12.1)	NA	59 (12.1)	NA	
10-20	125 (25.7)	NA	125 (25.7)	NA	
20	262 (53.8)	NA	262 (53.8)	NA	

^I pvalue from chi-square test when categorical and Kruskal-Wallis test when continuous.

ASA, American Society of Anesthesiologists; BMI, body mass index; IQR, interquartile range; NA, not applicable.

Table 2

Logistic regression analyses for the associations between individual smoking characteristics and advanced disease (AJCC stage 3) among patients with clear cell renal cell carcinoma

Smoking Characteristics	OR (95% CI)	p Value
Smoking status		0.062
Never		
Former	1.34 (1.05–1.72)	
Current	1.07 (0.78–1.47)	
Pack-years		0.036
<20		
20+	1.43 (1.02–2.00)	
Years since quitting		0.622
Current		
<10	1.82 (0.73–4.55)	
10+	1.49 (0.65–3.44)	

AJCC, American Joint Committee on Cancer; I, confidence interval; OR, odds ratio.

Table 3

Multivariable competing risks regression analysis for the association between smoking status and cancer-specific death, with death from other causes treated as a competing event

	Cancer-Specific Death		Death from Other Causes	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age at surgery	1.00 (0.99–1.02)	0.870	1.08 (1.06–1.10)	<0.001
Sex		0.250		0.940
Male	Ref		Ref	
Female	0.75 (0.46–1.22)		1.01 (0.75–1.37)	
ASA		0.580		<0.001
Healthy	Ref		Ref	
Not healthy	1.13 (0.74–1.71)		1.88 (1.39–2.54)	
AJCC stage		<0.001		0.400
1–2	Ref		Ref	
3–4	3.35 (2.25–4.98)		1.15 (0.83–1.58)	
Grade		<0.001		0.210
1–2	Ref		Ref	
3–4	4.00 (2.58–6.20)		0.82 (0.60–1.12)	
Smoking status		0.290		0.003
Never	Ref		Ref	
Former	1.26 (0.80–1.98)		1.43 (1.04–1.96)	
Current	1.50 (0.89–2.52)		1.93 (1.29–2.88)	

AJCC, American Joint Committee on Cancer's, American Society of Anesthesiologists; I, confidence interval; HR, hazard ratio.