

Cigarette Smoking and Renal Cell Carcinoma

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The National Cancer Institute estimates that there will be 60,920 new cases of kidney cancer in the United States in 2011, and there will be a resulting 13,120 deaths.¹ According to the American Cancer Society, kidney cancer is the fifth most common cancer overall.² In the past 3 decades, the prevalence of renal cancer has been increasing steadily each year in the United States and Europe.

The association between cigarette smoking and cardiovascular and pulmonary diseases as well as numerous cancers has long been established. In the United States, smoking is indicated as the causative factor in 90% of lung cancer deaths in men and approximately 80% of lung cancer deaths in women.³ With the steadily increasing incidence of renal cell carcinoma (RCC) in recent years, more attention has been dedicated to the study of risk factors for this cancer in the attempt to gain insight on mechanisms of disease and potential strategies of prevention.

The risk factors associated with RCC include male gender, older age, renal insufficiency, cigarette smoking, hypertension, obesity, physical inactivity, and diabetes. Of note, cigarette smoking is among the few modifiable risk factors.⁴ Although cigarette smoking is a recognized risk factor for RCC, little data are available on the association between smoking history (ie, duration, intensity, cessation) and tumor characteristics and outcomes and the potential mechanisms are still poorly understood.⁵

More recent findings suggest that smoking is one of the most important risk factors for RCC. This is particularly true for patients with pre-existing renal disease and elderly men with hypertension. Furthermore, smoking may impair renal function in patients with apparently healthy kidneys and thus contribute to the risk of cancer.⁶

In this article we review and summarize the data

regarding the aspects of smoking that may be associated with RCC incidence and characteristics.

Suspected Mechanisms

Cigarettes smoke contains more than 45,000 chemicals (eg, nicotine, tar, ammonia, carbon monoxide, carbon dioxide, formaldehyde, acrolein, acetone, benzopyrenes, hydroxyquinone, nitrogen oxides, cadmium) many of which are known to be carcinogenic.⁷ This extreme range of potentially implicated toxic substances makes it difficult to attribute a specific substance key role in carcinogenesis. However, general mechanisms have been proposed and the role of nicotine has been extensively studied.

These toxins can increase cell turnover and induce DNA damage, which may be involved in carcinogenesis and cancer progression. In addition, cigarette smoking has been shown to be associated with a myriad of genetic and epigenetic abnormalities such as gene mutation, deletions, and DNA methylation. Furthermore, smoking may promote an inflammatory state by creating a relatively hypoxic environment, and it may suppress immune response. The combination of the above listed effects could facilitate emerging neoplastic clones by providing them an adequate environment, furthermore, suppression of immune system control removes part of the regulation of cell proliferation and proinflammatory and angiogenic effects actively support the neoplastic process.

The Role of Nicotine

The proangiogenic effects of nicotine may promote tumor growth. Nicotine has been shown to stimulate endothelial cell tube formation via pathways mediated by the angiogenic growth factors such as basic fibroblast growth factor (bFGF) or vascular endothelial growth factor (VEGF). Nicotine was shown to induce bFGF but not VEGF release from human endothelial cells. Nicotine effectively promoted the generation of new blood vessels from existing ones in a chorioallantoic membrane (CAM) model, and doubled tumor growth in the CAM

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tumor implant model regardless of the tumor type indicating nontumor-specific promotion of growth via shared angiogenic pathways.⁸

Nicotine has been shown to induce angiogenesis in a number of other models. In a study by Heeschen and colleagues,⁹ tumor growth was markedly accelerated in the nicotine group and corresponded with increased vascularization of the tumor tissue. The researchers observed significantly higher capillary density in the tumors from mice exposed to nicotine 1.1 (95% CI 0.8-1.7) versus 0.2 (0.1-0.4) capillaries/kilopixel; $P < .001$. In another experiment, Lewis lung cancer cells were orthotopically implanted into the animal lung parenchyma. Tumor vascularization was again significantly higher in the nicotine group: 1.8 capillaries/kilopixel (95% CI 0.9-2.5) versus 0.5 capillaries/kilopixel (95% CI 0.2-0.9); $P < .001$. The systemic levels of VEGF were also significantly higher in the nicotine group compared with controls: 54.1 (95% CI 170.0-225.7) pg/mL; $P < .001$.

Another interesting aspect is that nicotine increases sympathetic activity via direct stimulation of postganglionic sympathetic nerve endings. Smoking a single cigarette markedly increases plasma concentration of norepinephrine and epinephrine in healthy volunteers, whereas postganglionic muscle sympathetic nerve traffic decreases significantly. Thus, nicotine triggers catecholamine release from peripheral sympathetic nerve endings and the adrenal medulla. This increased sympathetic activity may represent yet another mechanism involved.⁶

Nicotine is only one of the numerous substances contained in cigarette smoke. The extensive research into nicotine's effect, however, shows that a variety of pathways and molecular mechanisms may be of importance with regard to renal carcinogenesis.

Smoking and Hypertension

Smoking is an especially high renal risk factor in hypertensive patients. The exact mechanisms have not yet been elucidated, although increase in blood pressure, alteration of intrarenal hemodynamics, as well as activation of the sympathetic nerve, the renin-angiotensin, and the endothelin systems could represent potential mechanisms of smoking-induced renal damage. In patients with primary hypertension proteinuria has been found in 4% to 18% of patients and albuminuria in 10% to 25% of patients and smoking increased this risk.¹⁰

Hörner and colleagues¹¹ found that smoking was the strongest predictor for albuminuria in patients with primary hypertension. Halimi and colleagues¹² reported on results from a study that included 28,409 subjects. Their findings show an increased risk of irreversible proteinuria that may occur despite moderate smoking. Hypertension and functional damage to the kidney may play a concerted role in forming the ground for renal carcinogenesis. The notion that smoking effects may be more pronounced in men and the elderly⁶ is in line with

male predominance and older age association of RCC, which suggests intricate relationships between the different risk factors.

Current Smokers Versus Past Smokers Versus Never Smokers

Although there is considerable evidence for the link between cigarette smoking and increased risk of RCC, the results of a meta-analysis showed that the association between RCC risk and the duration of smoking is not as well established. The results from a study by Theis and colleagues¹³ showed that relative risk (RR) for RCC in smokers (current or past) was 1.38, and the risk was greater in men (RR = 1.50) than in women (RR = 1.27).⁵ When exposure was measured in pack-years, trends between RCC and smoking were stronger ($P = .014$). There was a 30% risk increase of RCC in smokers compared with never smokers. Moreover, the association was greater when smokers of 20 or more pack-years were compared with those of less than 20 pack-years, which suggests a dose-dependent effect of cigarette smoking on the risk of RCC.

While cigarette smoking is a risk factor, smoking cessation appears to reverse this association. Theis and colleagues,¹³ in a population-based study, found a trend of decreasing risk across 10-year smoking cessation intervals: those who had stopped smoking 11 to 20 years earlier had a 60% decrease in risk compared with current smokers.¹³

A drop in relative risk of RCC in long-term former smokers compared with patients who had recently stopped smoking was also reported by Hunt and colleagues.¹⁴ However, the results of their meta-analysis were not conclusive because of significant heterogeneity in the methods used to determine the length of smoking cessation in the evaluated studies.

Findings from a population-based case-control study suggest that long-term smoking cessation (20 or more years) reduces the risk of RCC to a level that is equal to that of never-smokers, even after adjustment for lifetime smoking intensity and duration. Shorter cessation periods (<10 years, 10 to 19 years) were associated with only moderate reductions in RCC risk. Multivariate adjustment for other risk factors for RCC did not alter the results. There was no evidence that showed that risk reduction associated with smoking cessation differed according to gender, BMI, or pack-years of smoking.¹⁵

Our group looked at the association between cigarette smoking and smoking cessation and RCC stage among patients undergoing surgery.¹⁶ In this large cohort of multiethnic patients, 207 (24.5%) had advanced disease and 638 (75.5%) had localized tumors. There were more men in the former and current smoker groups ($P < .001$). Advanced RCC was more frequent in former and current smokers (29.3% and 28.7%, respectively) compared with nonsmokers (20.2%; $P = .012$). Locally advanced disease (stage T3 or higher) was found in 16.3% of never smokers compared with 25.7% in current

and past smokers. After adjusting for covariates (age, ethnicity, sex, and personal and family history of cancer) cigarette smoking was still significantly associated with advanced RCC, which reinforces the importance of smoking as a risk factor not only for RCC but also specifically for pathological characteristics of kidney cancer portending worse prognosis. Moreover, in this study the deleterious associations were, at least in part, reversed by smoking cessation with long-term quitters approximating the risk of advanced disease of never smokers.

RCC Outcomes

Cigarette smoking may be associated with worse prognosis and higher disease-specific mortality for RCC. Parker and colleagues¹⁷ reported on 392 (17.5%) current cigarette smokers, 762 (34.0%) former smokers, and 1088 (48.5%) never smokers undergoing surgery for RCC. While their results were similar to our study results¹⁶ there were differences in disease stage at presentation, namely, current smokers were more likely to be symptomatic, have regional lymph node involvement (8% vs 4% and 5%; $P = .024$) and distant metastases (22% vs 13% and 13.5%; $P < .001$) as well as TNM stage IV disease (24% vs 14% and 15%; $P = .002$) compared with former and never smokers. Analyzing survival of these patients following surgery, the authors found that current smokers were 31% more likely to die from RCC compared with never smokers. However, after adjusting for TNM stage and nuclear grade, the association with current cigarette smoking was no longer apparent, suggesting that disease characteristics in smokers were likely responsible for the worse outcomes.¹⁷

As reported by Colli and associates,¹⁸ smoking, obesity, hypertension and physical inactivity are directly associated with RCC incidence. Moreover, smoking, obesity and physical inactivity were reportedly correlated to RCC mortality. These findings emphasize the importance of smoking as a risk factor beyond cardiovascular disease and indicate the potential impact of smoking on tumor features that denote more aggressive phenotype with consequent worse prognosis and higher disease-specific mortality rates.

Differences in Gender

Recent data indicate that men may be more susceptible to smoking-induced renal damage than women. The results of a population-based, cross-sectional study of 11,247 adults showed that smoking was independently associated with renal impairment in men (odds ratio [OR] = 3.59) but not in women.¹⁹ Gender-dependent effects, shown for renal functional damage, appear to be consistent for renal carcinogenesis as well.

Flaherty and colleagues²⁰ studied the association between hypertension, thiazide use, body mass index, weight change, and smoking and risk of RCC in 2 large cohorts: the Nurses' Health Study and the Health Professionals Follow-up Study. Their findings indicate that the risk associated with smoking may have different

magnitudes among men and women. The results of the study also show a clear dose-response with pack-years of smoking in men, but not in women. Although smoking as a risk factor for RCC is listed as a consistent factor by both the International Agency for Research on Cancer and the US Surgeon General, data from the study by Flaherty and colleagues²⁰ suggest different magnitudes of this association across genders. This intriguing finding should be explored further to elucidate the differential pathways that may help in understanding the molecular mechanisms behind smoking-induced renal damage and carcinogenesis.

Summary

Cigarette smoking continues to be the leading cause of preventable morbidity and mortality in the United States.²¹ It is responsible for nearly 20% of all deaths each year.²² Tumors of the urinary bladder, larynx, esophagus, colon and rectum, and kidney have all been linked to cigarette smoking.

The evidence is clear that cigarette smoking contributes significantly to the increased risk of RCC. Smoking intensity, duration and total exposure are associated with increased risk of RCC. There is evidence that smoking cessation may revert this association and, with durable smoking cessation, bring the risk of kidney cancer to that of never smokers.

Smoking cessation should be emphasized not only for prevention of cardiovascular and pulmonary diseases but also because of the consequences of smoking on renal function and kidney carcinogenesis. In fact, cigarette smoking is one of the modifiable risk factors for RCC that can be acted upon on personal and population levels. As such, the adoption of smoking prevention cessation strategies should be encouraged.

In conclusion, cigarette smoking is an independent risk factor for RCC. Higher intensity, longer duration of smoking, and greater cumulative exposure are associated with an increase in the risk of RCC and specifically, advanced disease that portends worse prognosis. Smoking cessation has been shown to reduce these associations. Despite suggestions of gender-dependent effects of smoking on RCC risk, smoking cessation benefits are seen across genders. Given the established link between cigarette smoking and RCC, the importance of smoking cessation should be reinforced. Despite accumulating data, there are still unfilled gaps in our understanding of the pathways involved and more detailed connections between smoking and RCC. Specifically, it has been suggested that smokers are at increased risk of RCC-specific mortality, and presentation at advanced stage. It may be that smoking, and compounds contained in cigarette smoke, fuel cancer growth via proinflammatory and proangiogenic effects. However, more research is needed to elucidate the effects of smoking and its cessation on RCC outcomes and prognosis, as well as to help in understanding the mechanisms that result in a more aggressive RCC phenotype in smokers.

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