Smoking Cessation After Diagnosis of Kidney Cancer Is Associated With Reduced Risk of Mortality and Cancer Progression: A Prospective Cohort Study

Mahdi Sheikh, MD, PhD[1]; Anush Mukeriya, MD[2]; Hana Zahed, MSc[1]; Xiaoshuang Feng, PhD[1]; Hilary A. Robbins, PhD[1]; Oxana Shangina, PhD[2]; Vsevolod Matveev, MD[3]; Paul Brennan, PhD[1]; and David Zaridze, MD, PhD[2]

PURPOSE To investigate whether postdiagnosis smoking cessation may affect the risk of death and disease progression in patients with renal cell carcinoma (RCC) who smoked at the time of diagnosis.

METHODS Two hundred twelve patients with primary RCC were recruited between 2007 and 2016 from the Urological Department in N.N. Blokhin National Medical Research Center of Oncology, Moscow, Russia. Upon enrollment, a structured questionnaire was completed, and the patients were followed annually through 2020 to repeatedly assess their smoking status and disease progression. Survival probabilities and hazards for all-cause and cancer-specific mortality and disease progression were investigated using extended the Kaplan-Meier method, time-dependent Cox proportional hazards regression, and Fine-Gray competing-risk models.

RESULTS Patients were followed for a median of 8.2 years. During this time, 110 cases of disease progression, 100 total deaths, and 77 cancer-specific deaths were recorded. Eighty-four patients (40%) quit smoking after diagnosis. The total person-years at risk for this analysis were 748.2 for continuing smoking and 611.2 for quitting smoking periods. At 5 years of follow-up, both overall survival (85% v 61%) and progression-free survival (80% v 57%) rates were higher during the quitting than continuing smoking periods (both $P <$ .001). In the multivariable time-dependent models, quitting smoking was associated with lower risk of all-cause mortality (hazard ratio [HR], 0.51; 95% CI, 0.31 to 0.85), disease progression (HR, 0.45; 95% CI, 0.29 to 0.71), and cancer-specific mortality (HR, 0.54; 95% CI, 0.31 to 0.93). The beneficial effect of quitting smoking was evident across all subgroups, including light smokers versus moderate-heavy smokers and those with early-stage versus late-stage tumors.

CONCLUSION Quitting smoking after RCC diagnosis may significantly improve survival and reduce the risk of disease progression and cancer mortality among patients who smoke.

INTRODUCTION

An estimated 430,000 individuals were diagnosed with kidney cancer and 180,000 died of this disease in 2020.[1] The burden of kidney cancer is higher in North America, Europe, and Oceania, where it ranks among the top 10 most common cancers.[1]

Smoking is a known cause of kidney cancer[2] and is estimated to account for 17% of the kidney cancer burden worldwide.[3] Approximately 15%-20% of patients with kidney cancer are active smokers at diagnosis.[4,5] Although studies have shown that quitting smoking can reduce the risk for developing kidney cancer,[6,7] evidence is limited on whether smokers can still benefit from quitting smoking after the diagnosis of kidney cancer. Limited evidence from retrospective studies indicates better survival among patients with kidney cancer who are former smokers than current smokers.[8-12] However, these studies are not conclusive as they have major limitations in their exposure assessment methods.

Particularly, smoking data in these studies were either extracted from medical records or collected once at the time of diagnosis or treatment without accounting for the time of smoking cessation or later changes in smoking behavior.[8-13] Furthermore, there is no evidence on whether any effects of quitting smoking could vary between light versus moderate-heavy smokers and patients with early-stage versus late-stage kidney cancer.

We conducted a prospective study of patients who were newly diagnosed with kidney cancer and repeatedly assessed smoking behavior during an average follow-up of 8 years to investigate whether postdiagnosis smoking cessation could affect the risk of death and disease progression among these patients.

METHODS

Study Population and Design

This study included patients with newly diagnosed primary renal cell carcinoma (RCC) who were originally

CONTEXT

Key Objective
Approximately 15%-20% of patients with kidney cancer are active smokers at diagnosis. In this study, we aimed to investigate whether quitting smoking could affect the risk of death and disease progression among patients with kidney cancer who smoke.

Knowledge Generated
Patients with kidney cancer who smoked at diagnosis were more likely to die when they continued smoking than when they quit smoking after diagnosis (24% v 6% at 3 years; 39% v 15% at 5 years). Quitting smoking after the diagnosis of kidney cancer was associated with almost 50% lower risk for death and 56% lower risk for disease progression. The beneficial effects of smoking cessation were evident across all patient subgroups, including those with early-stage versus late-stage tumors and patients who were light smokers versus moderate-heavy smokers at diagnosis.

Relevance (M.A. Carducci)
Although the findings of this report seem intuitive, this paper is important because there is a paucity of evidence that details the effects of cessation after cancer diagnosis. Interventions that support patients in their efforts to stop smoking should be encouraged to improve overall progression outcomes.*

*Relevance section written by JCO Associate Editor Michael A. Carducci, MD, FACP, FASCO.

enrolled to a large prospective cohort study of kidney cancer survival in Russia. Participants were enrolled between March 2007 and June 2016 from the Urological Department in the N.N. Blokhin National Medical Research Center of Oncology, Moscow, Russia. The inclusion criteria were residing in Moscow region; having histologically confirmed RCC; not having undergone any previous local or systemic treatment (diagnostic biopsies excluded) for the current tumor; and being a current smoker at the time of diagnosis, which was defined as smoking at least one cigarette per day within the past year before the time of diagnosis. All participants provided written informed consent at enrollment. The study was approved by the ethical committees of the International Agency for Research on Cancer and the Blokhin National Medical Research Center of Oncology.

Baseline Interviews and Questionnaire Data

The participants were interviewed using a structured questionnaire that contained detailed questions on demographics, behavioral factors, different exposures, and health conditions including chronic kidney disease, hypertension, and diabetes mellitus. Height and weight were measured, and BMI was calculated.

Participants were asked about lifetime smoking history, which included queries about the duration and frequency of smoking cigarettes, as well as the average number of cigarettes smoked every day. Participants were also asked about lifetime history of regular alcohol drinking, which is defined as drinking alcoholic beverages at least once a week for 1 year.

Baseline Tumor Data

An expert local team was asked to review all relevant medical documents and complete a questionnaire that included information on the clinical and histopathologic features of the tumor and the existing illness. A central team at the International Agency for Research on Cancer performed regular quality control checks to ensure the quality of the filled questionnaires and data. The classification of tumor stage was performed using the medical documents at the time of diagnosis and before receiving any treatment, on the basis of the 7th edition of the TNM classification system that is proposed by the American Joint Committee on Cancer.[14]

Follow-Up Data on Smoking, Clinical Interventions, and Disease Status

The participants were followed annually to record any changes in their smoking behavior and disease status. At each follow-up, the participants or their families were contacted and asked about quitting smoking and, when applicable, the time of smoking cessation. Participants were considered as smoking quitters if they reported to have quit smoking completely during the follow-up time. Otherwise, participants were categorized as continued smokers. During each follow-up, queries were made to collect detailed information on tumor progression, therapeutic interventions, and vital status. When applicable, the corresponding medical records were also reviewed by a local team to determine disease progression. Furthermore, the cohort data are linked to the Moscow cancer and death registries, to minimize the possibility of misclassifications in the outcomes and to record the primary and secondary causes of death, which was done according to the 10th Revision of the International Statistical Classification of Diseases and Related Health Problems.[15]

Statistical Analysis

Because participants quit smoking at different time points during the follow-up, we treated quitting smoking as a time-dependent variable in all analyses.[16-21] In this

approach, data from participants who quit smoking during the follow-up contribute differently than those who continued smoking. Particularly, for participants who quit smoking after diagnosis, the follow-up time is divided into subperiods, where each switch in smoking status (quitting or relapsing smoking) initiates a new subperiod.[16-21] For participants who quit smoking, the value of the time-dependent variable is 0 before the time of quitting and changes to 1 from the time of quitting smoking and onward. For those who continued smoking, the value remains 0 during the follow-up. For participants who quit and then relapsed smoking, the value of the time-dependent variable is 0 before the time of quitting and after the time of relapsing smoking.[16-21]

We used extended Kaplan-Meier curves and Mantel-Byar tests to describe the probability of survival during the continuing smoking and quitting smoking periods.[16-18] We used time-dependent Cox proportional hazards regression models to investigate the association between quitting smoking and hazards of death and disease progression.[19,20] We further used Fine-Gray competing-risks regression models that account for death from other causes as the competing event, to evaluate the association between quitting smoking and hazards of kidney cancer–specific death.[21]

In all models, we defined entry time as the date the participant was diagnosed with RCC, and date of the last contact was defined as the censoring date for participants who were alive at the last contact (through September 12, 2020). For participants who quit smoking during the follow-up, a subperiod that followed smoking after diagnosis was considered as starting at baseline and censored at the time of smoking cessation. Consequently, a subperiod that followed a switch to quitting smoking was considered left-truncated at the time of the switch. To assess the probability of overall survival and hazards of overall mortality, we defined end of follow-up as the date of death from any cause. To assess progression-free survival, we defined end of follow-up time as the date of death from any cause or date of tumor progression (local recurrence or metastasis), whichever occurred first. To assess kidney cancer–specific mortality, we defined end of follow-up time as the date of death from kidney cancer for the event of interest, and date of death from any other cause as the competing event.

The regression models were adjusted for age at diagnosis, sex, chronic health conditions, pack-years of cigarettes smoked, regular alcohol drinking status, tumor stage at diagnosis, and treatments received at the follow-up. All participants underwent surgery, while 34 received targeted therapy, and 12 received immunotherapy. Therefore, we combined targeted therapy and immunotherapy into one treatment variable. Further adjustments for year of diagnosis, education level, BMI at diagnosis, and tumor histology did not change the obtained estimates (Data Supplement, online only). Therefore, we did not include these variables in the main models. Five participants had

missing data for the predictor variables and were therefore excluded from this analysis. For each model, we tested the proportional hazards assumption using Schoenfeld's global test, which was met for all variables in the multivariable models, except for tumor stage and treatment, which showed time-varying effects in some models and were therefore treated as time-varying covariates.[22]

To account for potential confounders that might affect the survival estimates during the continuing and quitting smoking periods, we separately plotted the adjusted survival curves for each RCC stage. These curves were derived from the adjusted time-dependent regression models where the continuous variables were set at the median values and the categorical variables were set at the reference categories.[23,24]

We performed stratified analyses and used interaction tests to assess whether the effects of quitting smoking are different across the strata of light smokers (smoked ≤26 pack-years at baseline) versus moderate-heavy smokers (smoked >26 pack-years at baseline), and patients with early-stage (I, II) versus late-stage (III, IV) RCC. For each stratum, we also assessed the association between quitting smoking and the overall survival using the extended Kaplan-Meier method and Mantel-Byar test (quitting smoking was treated as a time-dependent variable).

Since survivorship bias is the main concern in assessing the effect of exposures that vary over time, in addition to using a time-dependent variable for quitting smoking in the main analyses, we performed two sensitivity analyses by excluding participants who quit smoking after 3 and 12 months of diagnosis (ie, participants who survived longer and had more chance to quit smoking).

The type 1 error rate was set at 5% and the statistical analyses were two-sided. The data were analyzed using Stata statistical software version 17.0 (Stata Corporation, College Station, TX).

RESULTS

The study recruited 228 currently smoking patients with kidney RCC. Of these, 16 were excluded because of missing data for the predictor variables (n = 5), having unknown histology (n = 2), or having non–renal cell kidney tumors (n = 9). The remaining 212 current smoker patients with RCC were included in this analysis and none of them were lost to follow-up. The total person-years at risk for this analysis were 748.2 for continuing smoking and 611.2 for quitting smoking periods.

At enrollment, the median age for the included participants was 56.1 years (IQR, 50.4-60.8) and the median BMI was 27.4 (IQR, 24.1-31.4); 80% of the participants were male and 59% had a university degree. More than half of the participants (54%) were diagnosed with stage I tumors, and only few participants underwent targeted therapy (n = 34) or immunotherapy (n = 12; Table 1).

TABLE 1. Baseline Demographical and Clinical Features Among All Patients, and the Subgroups of Patients Who Continued Smoking and Quit Smoking During the Follow-Up

Variable	All Participants	Participants Who Continued Smoking During the Follow-Up	Participants Who Quit Smoking During the Follow-Up[a]
No. of participants			
No. (%)	212	128 (60)	84 (40)
Age, years			
Median (IQR)[b]	56.1 (50.4-60.8)	56.7 (51.2-60.7)	54.8 (49.8-61.1)
Sex, No. (%)			
Male	170 (80)	102 (80)	68 (81)
Female	42 (20)	26 (20)	16 (19)
Education, No. (%)			
Less than high school	55 (26)	37 (29)	18 (22)
High school degree	31 (15)	19 (15)	12 (14)
University degree	126 (59)	72 (56)	54 (64)
BMI			
Median (IQR)	27.4 (24.1-31.4)	27.2 (23.4-30.8)	27.6 (25.0-32.7)
Chronic diseases, No. (%)[b]			
No	128 (60)	74 (58)	54 (64)
Yes	84 (40)	54 (42)	30 (36)
Regular alcohol drinking, No. (%)			
Never	134 (63)	76 (60)	58 (69)
Former	19 (9)	13 (10)	6 (7)
Current	59 (28)	39 (30)	20 (24)
Cumulative cigarettes smoked			
Median (IQR) (pack-years)[b]	26.5 (17-37)	27.9 (19.5-38.8)	24.2 (13.8-34)
Histology, No. (%)			
Clear cell RCC	181 (85)	110 (86)	71 (85)
Other subtypes RCC	31 (15)	18 (14)	13 (15)
Tumor stage, No. (%)			
I	114 (54)	60 (47)	54 (64)
II	16 (7)	9 (7)	7 (8)
III	48 (23)	35 (27)	13 (16)
IV	34 (16)	24 (19)	10 (12)
Targeted therapy, No. (%)			
No	178 (84)	104 (81)	74 (88)
Yes	34 (16)	24 (19)	10 (12)
Immunotherapy, No. (%)			
No	200 (94)	120 (94)	80 (95)
Yes	12 (6)	8 (6)	4 (5)

Abbreviation: RCC, renal cell carcinoma.

[a]Data from participants who quit smoking during the follow-up contributed differently to the main analysis than those who continued smoking. For those who quit smoking during the follow-up time, the follow-up period was divided into subperiods of before and after quitting smoking.

[b]Chronic diseases include hypertension, diabetes, and chronic kidney disease.

During the follow-up, 84 participants (40%) reported to have quit smoking, none of whom reported relapsing during the follow up period, while 128 participants (60%) reported to have continued smoking after their diagnosis.

Participants who quit versus continued smoking during the follow-up were similar across a range of demographic, behavioral factors, and clinical variables at the time of recruitment (Table 1). Of the 84 quitters, 47 (56%) quit
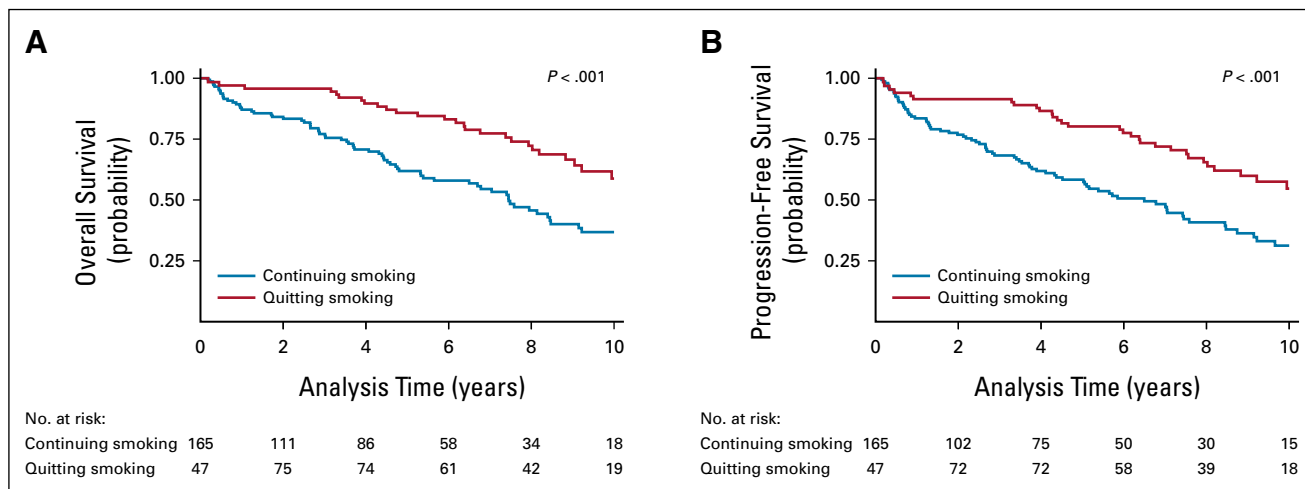
FIG 1. Extended Kaplan-Meier curves illustrating the probability of (A) overall survival (B) progression-free survival among smoker patients with renal cell carcinoma during the quitting smoking versus continuing smoking periods. *P* values were obtained from the Mantel-Byar test for comparing time-dependent survival data.

shortly after diagnosis and before the time of receiving the first treatment, 30 (36%) quit after treatment initiation but during the first year after diagnosis, and seven (8%) quit after the first year of diagnosis (Data Supplement).

At follow-up, mortality and disease progression occurred less often during periods in which the patients quit smoking than when they continued smoking ($P < .001$; Fig 1). The estimated probabilities of overall and progression-free survivals at 3 years were higher during the quitting than continuing smoking periods (overall survival, 94% *v* 76%; progression-free survival, 90% *v* 67%; $P < .001$ for both; Table 2; Fig 1). Similarly, at 5 years, the probabilities of overall and progression-free survivals were higher during the quitting than continuing smoking periods (overall survival, 85% *v* 61%; progression-free survival, 80% *v* 57%; $P < .001$ for both; Table 2; Fig 1). The higher probability of survival during the smoking cessation period was evident across all patient subgroups, including light

smokers ($P = .007$; Data Supplement), moderate-heavy smokers ($P = .013$; Data Supplement), and patients with early-stage ($P = .025$; Data Supplement) and late-stage ($P = .048$; Data Supplement) tumors.

In the multivariable time-dependent regression models, quitting smoking after the diagnosis of cancer was associated with lower risk of all-cause mortality (hazard ratio [HR], 0.51; 95% CI, 0.31 to 0.85), disease progression (tumor recurrence, metastasis, or death; HR, 0.45; 95% CI, 0.29 to 0.71), and kidney cancer–specific death (HR, 0.54; 95% CI, 0.31 to 0.93; Table 3). The beneficial effects of quitting smoking on the hazards of death and disease progression remained comparable after excluding participants who quit smoking after 12 and 3 months of diagnosis (Table 3). In the stratified analyses, quitting smoking was similarly beneficial for light smokers versus moderate-heavy smokers (Data Supplement), and also for patients with early-stage versus late-stage tumors (Data Supplement).

TABLE 2. Estimates of Survival Among Patients With Renal Cell Carcinoma Who Smoked at the Time of Diagnosis, During Periods of Continued Smoking Compared With Periods of Smoking Cessation

Parameter	Continuing Smoking Period	Smoking Cessation Period	*P*a
Person-years at risk	748.2	611.2	
Overall survivalb			<.001
Probability of survival at 3 years (95% CI)	0.76 (0.68 to 0.82)	0.94 (0.85 to 0.97)	
Probability of survival at 5 years (95% CI)	0.61 (0.52 to 0.69)	0.85 (0.75 to 0.91)	
Progression-free survivalb			<.001
Probability of survival at 3 years (95% CI)	0.67 (0.58 to 0.74)	0.90 (0.80 to 0.95)	
Probability of survival at 5 years (95% CI)	0.57 (0.48 to 0.65)	0.80 (0.69 to 0.87)	

aP values were obtained from the Mantel-Byar test for comparing time-dependent survival data.

bEstimates are derived from extended Kaplan-Meier curves where smoking cessation was treated as a time-varying variable to account for the time of quitting smoking and the patients' switching between continued smoker and smoking quitter groups during the follow-up time.

TABLE 3. The Association Between Postdiagnosis Smoking Cessation and Different Outcomes Among Patients With Renal Cell Carcinoma Who Smoked at Diagnosis

Outcome/Exposure Feature	HR (95% CI)		
	All-Cause Mortality[a]	Disease Progression[a,b]	Cancer-Specific Mortality[a,c]
All participants included			
No. of outcome events	100	110	77
Quitting[d] *v* continuing smoking	0.51 (0.31 to 0.85)	0.45 (0.29 to 0.71)	0.54 (0.31 to 0.93)
Excluding participants who quit smoking within 12 months after diagnosis			
No. of outcome events	97	107	75
Quitting[d] *v* continuing smoking	0.51 (0.30 to 0.85)	0.45 (0.28 to 0.71)	0.57 (0.31 to 1.02)
Excluding participants who quit smoking within 3 months after diagnosis			
No. of outcome events	92	101	72
Quitting[d] *v* continuing smoking	0.55 (0.31 to 0.95)	0.48 (0.29 to 0.79)	0.75 (0.41 to 1.37)

Abbreviation: HR, hazard ratio.

[a]The estimates are derived from time-dependent regression models that are adjusted for age at diagnosis, sex, history of chronic diseases, cumulative cigarettes smoked, alcohol drinking status, tumor stage, and treatment (targeted therapy/immunotherapy).

[b]Progression is defined as local recurrence, metastasis, or death from any cause.

[c]In this model, death from any cause other than kidney cancer was set as a competing event.

[d]Quitting smoking is treated as a time-varying exposure that accounts for quitting time and switching in smoking status during the follow-up period.

The estimated survival probabilities, which were derived from the adjusted time-dependent regression models, consistently showed higher overall and progression-free survival probabilities during the quitting than continuing smoking periods across all RCC stages (Fig 2; Data Supplement).

DISCUSSION

In this prospective cohort study, we followed 212 currently smoking patients with RCC for an average of 8 years, of whom 84 participants quit smoking during the follow-up time. At follow-up, the overall and cancer-free survival rates were significantly higher during the quitting than continuing smoking periods. Compared with continuing smoking, quitting smoking was consistently associated with lower hazards of death and disease progression. The beneficial effects of quitting smoking were evident among light smokers and moderate-heavy smokers, as well as among patients with early-stage and late-stage tumors.

To our knowledge, this is the first study that prospectively evaluates the effects of smoking cessation after diagnosis among smoker patients with kidney cancer. In this study, we repeatedly assessed smoking status during the follow-up and found that quitting smoking after diagnosis was associated with almost 50% lower risk for overall death, 46% lower risk for cancer-specific death, and 55% lower risk for disease progression compared with continuing smoking. Previous studies on this topic have been primarily retrospective studies that assessed the effects of smoking status at diagnosis on subsequent RCC survival. A meta-analysis of 14 studies with 343,993 patients with RCC showed that current smokers at diagnosis have almost 60% increased risk of death and around three times increased risk for having poorer progression-free survival than never smokers, while a subgroup analysis of two studies that had investigated the effects of former smoking showed no increased risk for mortality among those who had quit smoking before the time of diagnosis.[13] Another meta-analysis of 24 studies showed a higher risk for RCC incidence among both current (29%) and former (14%) smokers, while the risk for RCC death was 32% higher among current smokers and was null among former smokers.[6] A recent study by Kroeger et al[12] assessed the effects of smoking status at the time of starting targeted therapy on the survival of 1,980 patients with metastatic RCC, and reported a poorer survival among current smokers than never and former smokers. However, similar to other previous studies, smoking status was retrospectively obtained from medical charts or screening forms, and the time of smoking cessation could not be reliably determined.[12]

Of all smoker patients in this cohort, 60% continued smoking through the course of their disease, leading to a significant number of extra deaths and progression events. Our results show that the benefits of quitting smoking (which is potentially feasible for all patients and could benefit patients financially) may be similar or even superior to the emerging targeted and immunotherapy treatments that are expensive, require specialized settings, and cannot be accessed by many patients.[25,26] We previously observed a similarly significant effect for postdiagnosis smoking cessation on the survival of smoker patients with lung cancer.[27] This evidence highlights the need for collaborative efforts to implement smoking treatment as an integral part of cancer management in patients who smoke. This is particularly important as smoker patients with cancer might feel fatalistic or may not realize that the benefits of smoking
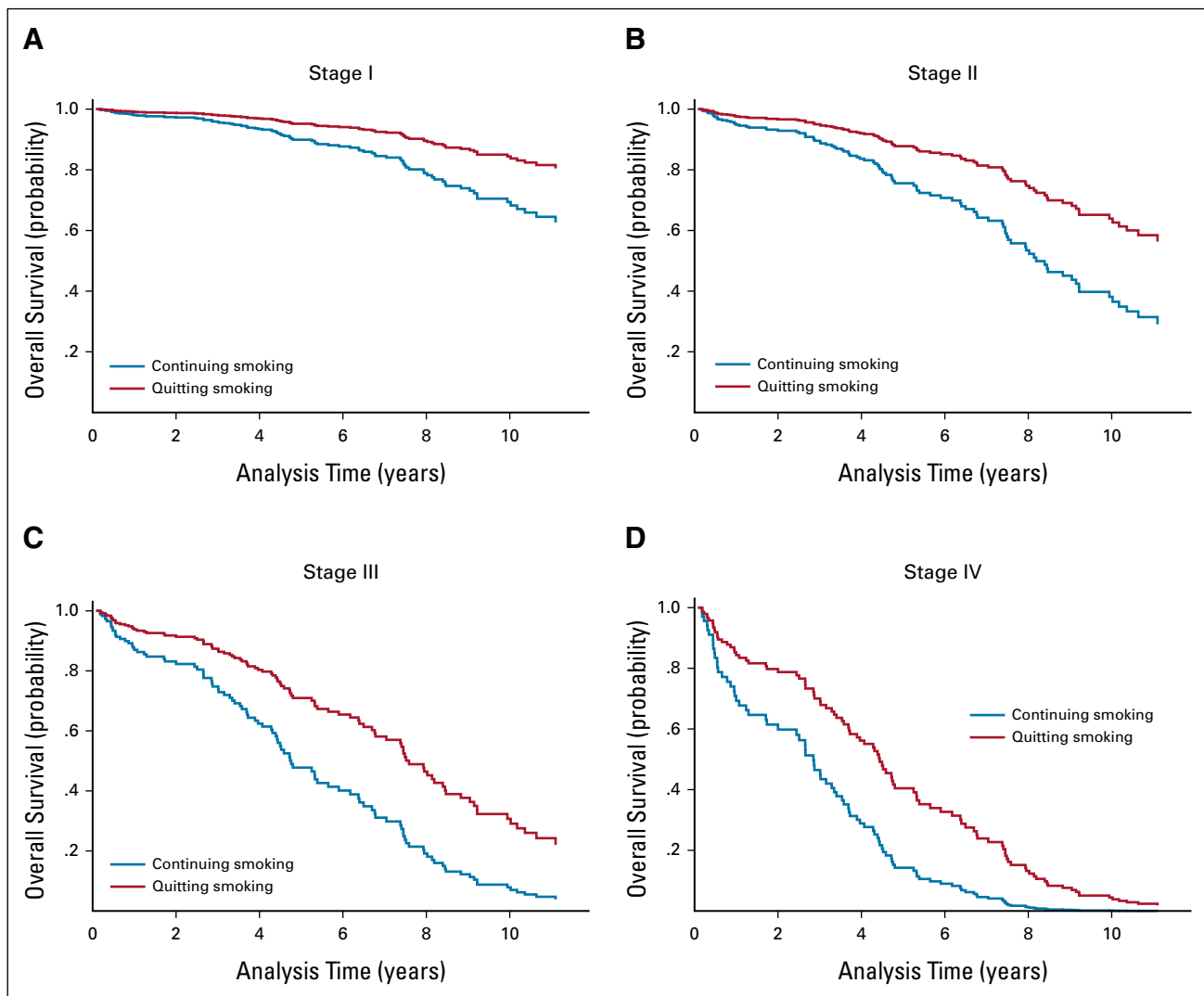
FIG 2. Adjusted survival curves illustrating the probability of overall survival during the quitting smoking versus continuing smoking periods in a 56-year-old male smoker with renal cell carcinoma (A) stage I, (B) stage II, (C) stage III, and (D) stage IV. Estimates are derived from adjusted time-dependent Cox regression models where smoking cessation was treated as a time-varying variable, the continuous covariates were set at the median value (age: 56, smoking: 26 pack-years), and the categorical variables were set at the reference category (male, without chronic health conditions, never regular alcohol drinker, and did not receive targeted/immunotherapy during the follow-up).

cessation apply even after cancer diagnosis. Furthermore, evidence shows that most smoker patients with cancer do not feel ready to quit after the diagnosis and there is still of subset of smoker patients with cancer who are not even recommended by their physicians to quit smoking.[28-31]

Several biologically plausible mechanisms have been suggested by which smoking can reduce survival in patients with cancer; cigarette smoke contains many carcinogens and mutagens that can directly affect tumor cells and increase their proliferation, migration, invasion, and angiogenesis.[32] Furthermore, smoking can impair the immune response to malignant growth,[32,33] affect the response to and complications from some cancer treatments,[34] and accelerate other illnesses including cardiovascular and other chronic diseases in patients with cancer.[34,35]

To our knowledge, this is the first study that prospectively investigates the effect of quitting smoking after diagnosis of kidney cancer on disease progression and survival rates with repeated assessments of smoking status during the follow-up and a long follow-up period. Also, to our knowledge, this is the first study that showed the beneficial effects of smoking cessation across different subgroups of patients with RCC on the basis of their baseline tumor stage and pack-years of cigarettes smoked. Finally, we used stringent statistical methods to address confounding and survivorship bias. This study also has some limitations including being an observational study with the possibility of measurement errors in the exposure and outcomes. Smoking status was based on self-report, which could have resulted in misclassification. However,

the prospective nature of the study and repeated assessment of smoking status could have minimized the possibility of inaccurate responses. Also, if there is any misclassification, it is anticipated to result from over-reporting smoking cessation, which consequently could bias the results toward the null. Another limitation of the current study is its small sample size for the subgroup analyses. Despite observing comparable estimates from the adjusted models across different strata, the estimates from the stratified analyses should be interpreted with caution as there were a small number of outcome cases in some of the strata.

In conclusion, this study provides strong evidence that quitting smoking after the diagnosis of kidney cancer can significantly improve the survival and reduce the risk of disease progression among these patients. Given that up to 20% of patients with kidney cancer are current smokers at diagnosis and most will continue to smoke afterward,[4,5] it is critical to integrate smoking treatment into the routine management of these patients.

AFFILIATIONS
[1]Genomic Epidemiology Branch, International Agency for Research on Cancer (IARC/WHO), Lyon, France
[2]Department of Epidemiology, N.N. Blokhin National Medical Research Centre of Oncology, Moscow, Russia
[3]Department of Urology, N.N. Blokhin National Medical Research Centre of Oncology, Moscow, Russia

CORRESPONDING AUTHOR
Mahdi Sheikh, MD, PhD, Genomic Epidemiology Branch, International Agency for Research on Cancer (IARC—WHO), 25 Avenue Tony Garnier, 69007 Lyon, France; Twitter: @mahdi_iarc; e-mail: sheikhm@iarc.who.int.

DISCLAIMER
Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer/World Health Organization.

PRIOR PRESENTATION
Presented in part as an abstract at the World Cancer Congress, Geneva, Switzerland, October 18-20, 2022.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.22.02472.

AUTHOR CONTRIBUTIONS
Conception and design: Mahdi Sheikh, Anush Mukeriya, Paul Brennan, David Zaridze
Administrative support: Mahdi Sheikh, Paul Brennan
Provision of study materials or patients: Anush Mukeriya
Collection and assembly of data: Mahdi Sheikh, Anush Mukeriya, Oxana Shangina, Vsevolod Matveev, Paul Brennan, David Zaridze
Data analysis and interpretation: Mahdi Sheikh, Anush Mukeriya, Hana Zahed, Xiaoshuang Feng, Hilary A. Robbins, Paul Brennan, David Zaridze
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71:209-249, 2021

2. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans: Tobacco smoke and involuntary smoking. IARC Monogr Eval Carcinog Risks Hum 83: 1-1438, 2004

3. Safiri S, Kolahi A-A, Mansournia MA, et al: The burden of kidney cancer and its attributable risk factors in 195 countries and territories, 1990–2017. Sci Rep 10: 13862, 2020

4. Tsivian M, Moreira DM, Caso JR, et al: Cigarette smoking is associated with advanced renal cell carcinoma. J Clin Oncol 29:2027-2031, 2011

5. Gansler T, Fedewa SA, Flanders WD, et al: Prevalence of cigarette smoking among patients with different histologic types of kidney cancer. Cancer Epidemiol Biomarkers Prev 29:1406-1412, 2020

6. Cumberbatch MG, Rota M, Catto JWF, et al: The role of tobacco smoke in bladder and kidney carcinogenesis: A comparison of exposures and meta-analysis of incidence and mortality risks. Eur Urol 70:458-466, 2016

7. Hunt JD, van der Hel OL, McMillan GP, et al: Renal cell carcinoma in relation to cigarette smoking: Meta-analysis of 24 studies. Int J Cancer 114:101-108, 2005

8. Sweeney C, Farrow DC: Differential survival related to smoking among patients with renal cell carcinoma. Epidemiology 11:344-346, 2000

9. Ehdaie B, Furberg H, Zabor EC, et al: Comprehensive assessment of the impact of cigarette smoking on survival of clear cell kidney cancer. J Urol 191:597-602, 2014

10. Keizman D, Gottfried M, Ish-Shalom M, et al: Active smoking may negatively affect response rate, progression-free survival, and overall survival of patients with metastatic renal cell carcinoma treated with sunitinib. Oncologist 19:51-60, 2014

11. Fajkovic H, Shariat SF, Klatte T, et al: Impact of smoking status on survival after cytoreductive nephrectomy for metastatic renal cell carcinoma. World J Urol 34: 1411-1419, 2016

12. Kroeger N, Li H, De Velasco G, et al: Active smoking is associated with worse prognosis in metastatic renal cell carcinoma patients treated with targeted therapies. Clin Genitourin Cancer 17:65-71, 2019

13. Xu Y, Qi Y, Zhang J, et al: The impact of smoking on survival in renal cell carcinoma: A systematic review and meta-analysis. Tumor Biol 35:6633-6640, 2014

14. Edge SB, Compton CC: The American Joint Committee on Cancer: The 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 17:1471-1474, 2010

15. WHO. International Classification of Diseases, 10th Revision (ICD-10). WHO, 2018. https://icd.who.int/browse10/2016/en

16. Snapinn SM, Jiang Q, Iglewicz B: Illustrating the impact of a time-varying covariate with an extended Kaplan-Meier estimator. Am Stat 59:301-307, 2005

17. Mantel N, Byar DP: Evaluation of response-time data involving transient states: An illustration using heart-transplant data. J Am Stat Assoc 69:81-86, 1974

18. Mi X, Hammill BG, Curtis LH, et al: Use of the landmark method to address immortal person-time bias in comparative effectiveness research: A simulation study. Stat Med 35:4824-4836, 2016

19. Shintani AK, Girard TD, Eden SK, et al: Immortal time bias in critical care research: Application of time-varying Cox regression for observational cohort studies. Crit Care Med 37:2939-2945, 2009

20. Zhou Z, Rahme E, Abrahamowicz M, et al: Survival bias associated with time-to-treatment initiation in drug effectiveness evaluation: A comparison of methods. Am J Epidemiol 162:1016-1023, 2005

21. Beyersmann J, Schumacher M: Time-dependent covariates in the proportional subdistribution hazards model for competing risks. Biostatistics 9:765-776, 2008

22. Bellera CA, MacGrogan G, Debled M, et al: Variables with time-varying effects and the Cox model: Some statistical concepts illustrated with a prognostic factor study in breast cancer. BMC Med Res Methodol 10:20, 2010

23. Jann B: Stata tip 8: Splitting time-span records with categorical time-varying covariates. Stata J 4:221-222, 2004

24. Ruhe C: Bootstrap pointwise confidence intervals for covariate-adjusted survivor functions in the Cox model. Stata J 19:185-199, 2019

25. Rao A, Wiggins C, Lauer RC: Survival outcomes for advanced kidney cancer patients in the era of targeted therapies. Ann Transl Med 6:165, 2018

26. Li P, Jahnke J, Pettit AR, et al: Comparative survival associated with use of targeted vs nontargeted therapy in Medicare patients with metastatic renal cell carcinoma. JAMA Netw Open 2:e195806, 2019

27. Sheikh M, Mukeriya A, Shangina O, et al: Postdiagnosis smoking cessation and reduced risk for lung cancer progression and mortality: A prospective cohort study. Ann Intern Med 174:1232-1239, 2021

28. D'Angelo H, Rolland B, Adsit R, et al: Tobacco treatment program implementation at NCI cancer centers: Progress of the NCI Cancer Moonshot-Funded Cancer Center Cessation Initiative. Cancer Prev Res 12:735-740, 2019

29. Fiore MC, D'Angelo H, Baker T: Effective cessation treatment for patients with cancer who smoke—The fourth pillar of cancer care. JAMA Netw Open 2:e1912264, 2019

30. Little MA, Klesges RC, Bursac Z, et al: Why don't cancer survivors quit smoking? An evaluation of readiness for smoking cessation in cancer survivors. J Cancer Prev 23:44-50, 2018

31. Golčić M, Tomaš I, Stevanović A, et al: Smoking cessation after a cancer diagnosis: A cross-sectional analysis in the setting of a developing country. Clin Pract 11:509-519, 2021

32. Sobus SL, Warren GW: The biologic effects of cigarette smoke on cancer cells. Cancer 120:3617-3626, 2014

33. de la Iglesia JV, Slebos RJC, Martin-Gomez L, et al: Effects of tobacco smoking on the tumor immune microenvironment in head and neck squamous cell carcinoma. Clin Cancer Res 26:1474-1485, 2020

34. Gemine R, Lewis K: Smoking cessation with lung cancer: Not too little, never too late! Eur Med J 4:86-91, 2016

35. Wang Y, Tao H, Paxton RJ, et al: Post-diagnosis smoking and risk of cardiovascular, cancer, and all-cause mortality in survivors of 10 adult cancers: A prospective cohort study. Am J Cancer Res 9:2493-2514, 2019

■ ■ ■

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Smoking Cessation After Diagnosis of Kidney Cancer Is Associated With Reduced Risk of Mortality and Cancer Progression: A Prospective Cohort Study

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Vsevolod Matveev
Honoraria: Ipsen, Bayer, AstraZeneca, Janssen, Astellas Pharma, MSD
Expert Testimony: BMS, Bayer, MSD, Janssen

No other potential conflicts of interest were reported.