Research Article

Risk for Renal Cell Carcinoma in Chronic Hepatitis C Infection

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Abstract

Background: Chronic infection with hepatitis C virus (HCV) confers increased risk for chronic renal disease, and numerous reports suggest an association with renal cell carcinoma (RCC), a cancer with rapidly rising global incidence. We sought to determine whether HCV infection confers an increased risk for developing RCC.

Methods: With the use of administrative data from a large, integrated, and ethnically diverse healthcare system, we did a cohort study of 67,063 HCV-tested patients between 1997 and 2006 who were followed for the development of RCC until April 2008.

Results: A search of the health system cancer registry for patients with the diagnosis of kidney cancer showed that RCC was diagnosed in 0.6% (17 of 3,057) of HCV-positive patients versus 0.3% (177 of 64,006) of HCV-negative patients. The mean age at RCC diagnosis was much younger in HCV-positive individuals (54 versus 63; $P < 0.001$). The univariate hazard ratio for RCC among HCV patients was 2.20 (95% confidence interval, 1.32-3.67; $P = 0.0025$). In a multivariate model that included the risk factors age, African-American race, male gender, and chronic kidney disease, the overall hazard ratio for RCC among HCV patients was 1.77 (95% confidence interval, 1.05-2.98; $P = 0.0313$).

Conclusion: Chronic HCV infection confers a risk for the development of RCC.

Impact: Clinicians should consider newly identified renal lesions in patients with chronic HCV infection with a heightened suspicion for neoplasm, and newly diagnosed cases of RCC may require more careful surveillance for the presence of HCV infection. Additional studies are required to confirm these findings and to explore potential mechanisms of oncogenesis. *Cancer Epidemiol Biomarkers Prev; 19(4); 1066–73. ©2010 AACR.*

Introduction

Globally, an estimated 170 million people are infected with chronic hepatitis C virus (HCV), a major cause of cirrhosis, liver failure, and hepatocellular carcinoma (1). Extrahepatic manifestations of chronic HCV infection include cryoglobulinemia, vasculitis, and various renal disorders (2). Among patients with HCV-mediated chronic kidney disease (CKD), HCV RNA and core protein have been isolated in kidney glomerular and tubular structures (3). The virus also has extrahepatic oncogenic potential because chronic HCV confers an increased risk of non-Hodgkin lymphoma and other hematopoietic malignancies (4), presumably through lymphoproliferative mechanisms (5).

The incidence of renal cell carcinoma (RCC) has increased rapidly over the past 2 decades, particularly among African Americans (6), and the reason for this rising incidence remains unexplained. Numerous reports have detailed this phenomenon, with increasing RCC rates described globally (7), and in the United States (6), Europe (8), Ireland (9), and Japan (10). Strong and reproducible risk factors for developing RCC have not been identified, but high body mass index, tobacco use, and, to a lesser extent, CKD have been implicated.

Within the past 5 years, several reports have linked HCV and RCC. Di Micco et al. (11) reported a cluster of five cases of RCC developing among HCV patients within a brief time frame and were the first to strongly suggest a renal oncogenic potential for HCV infection. Fayek et al. (12) in 2007 reported two cases of coexisting HCV and RCC in liver transplant candidates, and Garcia et al. (13) in 2007 reported synchronous hepatocellular carcinoma and RCC in a liver transplant recipient. In 2008 Rifkin (14) described a chronic hemodialysis patient with simultaneous HCV and RCC.

These case reports are consistent with our experience in treating patients with chronic HCV, several of whom have developed RCC. Thus, we did a cohort study by using administrative data from our health system to explore whether HCV infection confers an increased risk for developing RCC.

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Experimental Procedures

Study design and study sample

With the use of administrative data from Henry Ford Hospital, an integrated healthcare delivery system serving southeastern Michigan, we did a cohort study to establish whether the risk of RCC was increased among HCV-infected subjects. We compared adults (>18 y) who had at least one encounter with the health system (excluding persons undergoing laboratory testing within the system but not followed for care) and tested anti-HCV positive with a control cohort of patients who tested negative for anti-HCV. Our main outcome measure was the incidence of RCC in HCV-positive patients versus HCV-negative patients. The study was approved by the Institutional review Board at Henry Ford Hospital. Because this was a retrospective review with unidentified patients, there was no patient informed consent.

Diagnostic criteria

We defined seropositivity as a positive anti-HCV test (ELISA). We confirmed hepatitis C infectivity by a documented positive molecular assay for HCV RNA (HCV positive). Among the HCV-positive RCC patients, we recorded HCV RNA viral levels and genotypes, and liver histology, if available. We also attempted to establish estimated HCV disease duration by reviewing office encounters and, as applicable, recording year of blood transfusion or first year of injection drug use to represent the probable year of viral acquisition.

We included all HCV-positive cases identified between 1997 and December 2006. We established the diagnosis of RCC by examining the recorded documentation in the health system cancer registry between 1997 and April 2008. This registry records cancer both as established by anatomic pathology and as reported on imaging reports. Potential cancer cases for inclusion in the registry are identified by a review of all pathology and cytology reports. Cancer diagnosis codes in administrative databases [International Classification of Diseases, 9th ed., Clinical Modification (ICD-9-CM) codes in the range of 140 through 208.9] are also a source for registry case finding. Electronic medical records are used to confirm cancer diagnosis. The cancer registry data abstraction is completed by credentialed cancer registrars.

We confirmed all histologically diagnosed RCC by reviewing individual pathology reports, and we recorded RCC size and tumor type. The diagnoses of other cancers (colorectal, breast, prostate, lung, and hepatocellular) were also derived from the health system cancer registry. All confirmed RCC cases were incident cases, and we only included RCC cases if the cancer was diagnosed after the documentation of HCV RNA positivity.

We recorded demographic information, including age, gender, self-reported race, and body mass index, from a review of the administrative database. We defined the presence of CKD as being assigned an ICD diagnostic code for CKD or by having undergone dialysis during the study period. Presence of CKD was ascertained with the use of administrative data from patient encounters anytime during their care at our institution. The ICD-9-CM codes used were 585.xx (CKD) and V42.0 (history of kidney transplant).

Patient population

Between 1997 and 2006, 79,492 patients were tested for anti-HCV (Fig. 1). We excluded patients who had laboratory testing but no contact with the institution, were <18 y old, were diagnosed with RCC before 1997, had incomplete demographic data, or had positive tests for HIV or HBsAg, thus leaving an eligible population of 72,487 patients. We subsequently excluded 5,424 patients without confirmed viremia, meaning they were seropositive (anti-HCV positive) on ≥1 occasions for HCV, but were either (*a*) without nucleic acid technology confirmation of viral positive status, (*b*) negative for HCV RNA on ≥1 occasions, or (*c*) transiently anti-HCV positive. Our population for analysis included 64,006 HCV-negative patients and 3,057 HCV-positive patients. In a separate analysis, we excluded 7,109 patients with CKD to determine whether underlying kidney disease represented a confounding variable.

Abdominal imaging

To address the possibility of screening bias within the HCV-positive cohort, we examined the proportion of patients who underwent abdominal imaging during the analysis period. We considered any ultrasound, computed tomographic scan, or magnetic resonance imaging that included views of the liver and kidney as an abdominal imaging modality. We compared HCV positivity or negativity, as well as presence or absence of CKD.

Statistical methods

A *t* test was used to compare the mean age at baseline and kidney cancer diagnosis based on HCV status. In addition, *t* tests were used to compare group means for continuous data. χ^2 tests were used to compare race, gender, and presence of kidney disease.

Cox regression analysis with associated proportional hazards survival modeling was used to evaluate the ability of each study variable (HCV positivity, age, African-American race, male gender, and kidney disease) to predict kidney cancer outcome. Patients entered the cohort at testing for HCV and left the cohort at death, diagnosis of RCC, or last contact with the healthcare system. We did univariate and multivariate Cox modeling with age as a continuous variable, as well as separate modeling that included and excluded patients with CKD.

We did Kaplan-Meier analyses, both with and without the CKD population, to show the probability of remaining free from cancer during the cohort observation period until diagnosis of RCC, death, or date of last contact with the health system. The curves were calculated with the use of the product-limit method of estimation, with the various patient durations to either cancer onset or end
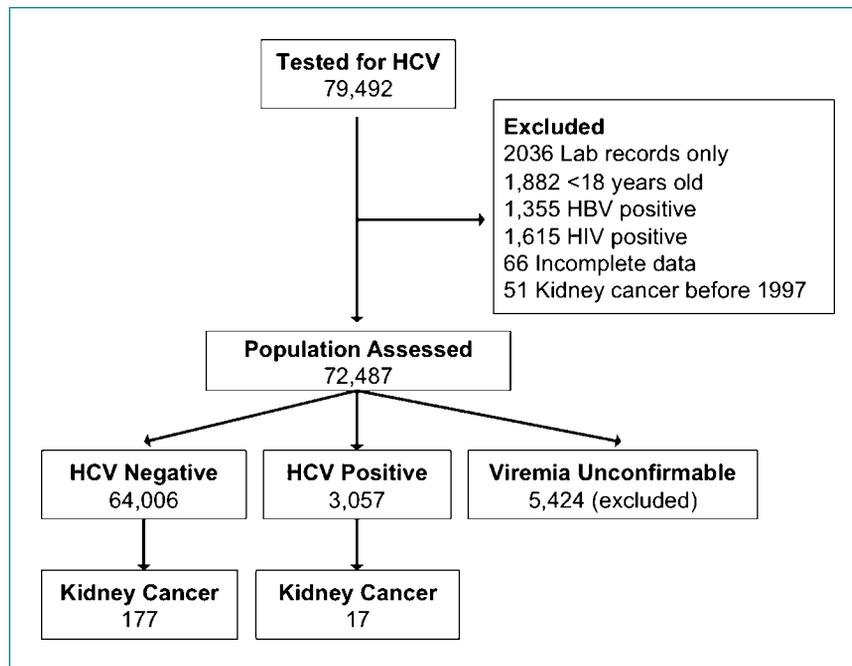
Figure 1. Determination of the study sample.

of follow-up used to calculate the probability of remaining free from kidney cancer at each follow-up time point.

Results

Study population

Among the study population of 67,063 patients, 3,057 (4.6%) were HCV positive (Table 1). The mean age of HCV-positive patients was older than that of seronegative patients (52 versus 48 y; $P < 0.001$). Men were more likely to be anti-HCV positive than women (5.8% versus 3.4%; $P < 0.001$). African Americans were more likely to be anti-HCV positive than non–African Americans (6.6% versus 3.1%; $P < 0.001$). Hepatitis C patients were more likely to have kidney disease than uninfected patients

(14.5% versus 10.4%; $P < 0.001$). No patients had cryoglobulinemia.

In the viremic cohort, as expected, the risk for development of hepatocellular carcinoma among HCV-seropositive patients was greatly increased: 27.5 of 1,000 in HCV-positive patients versus 1.4 of 1,000 in HCV-negative patients. The risks for colorectal cancer (2.9 of 1,000 versus 5.4 of 1,000 in HCV+ and HCV−, respectively), female breast cancer (22.5 of 1,000 versus 20.6 of 1,000), prostate cancer (13.1 of 1,000 versus 22.6 of 1,000), and lung cancer (5.9 of 1,000 versus 6.8 of 1,000) were not.

Characteristics of HCV-positive RCC patients

We reviewed the renal and hepatic histologies for the RCC patients in our study. Of the 17 RCC cases that

Table 1. Patient baseline characteristics

	HCV positive (n = 3,057)	HCV negative (n = 64,006)	Total (N = 67,063)
Age, y			
Mean (SD)	52 (10)	48 (17)*	48 (17)
Range	18-102	18-94	18-102
Race, n (%)			
African American	1,869 (61.1)	26,267 (41.0)*	28,136 (42.0)
Non–African American	1,188 (38.9)	37,739 (59.0)	38,927 (58.0)
Male gender, n (%)	1,903 (62.3)	30,878 (48.2)*	32,781 (48.9)
Kidney disease, n (%)[†]	443 (14.5)	6,666 (10.4)*	7,109 (10.6)

*$P < 0.001$.
[†]Diagnosis code for chronic kidney disease or dialysis status.

Table 2. Characteristics of RCC patients

	HCV positive (*n* = 17)	HCV negative (*n* = 177)
Age, y		
Mean (SD)	54 (11)	63 (12)*
Range	31-72	24-88
Race, *n* (%)		
African American	12 (70.6)	97 (54.8)
Non–African American	5 (29.4)	80 (45.2)
Male gender, *n* (%)	12 (70.6)	123 (69.5)
Kidney disease, *n* (%)	7 (41.2)	83 (46.9)
Renal histology, *n* (%)[†]		
Clear cell	8 (47.1)	92 (54.1)
Papillary	6 (35.3)	43 (25.3)
Mixed clear cell/papillary	2 (11.8)	9 (5.3)
Undifferentiated/other	1 (5.9)	26 (15.3)

*$P < 0.001$.
[†]Among the HCV-negative patients, 7 of 177 did not have RCC confirmed histologically.

were HCV positive, 8 were clear cell and 6 were papillary (Table 2). The mean RCC tumor diameter was 3.5 cm at diagnosis (range, 0.7-7.0 cm).

Among RCC patients with HCV who had liver biopsy information, eight had mild or no fibrosis, two had moderate fibrosis, and two had cirrhosis. Ten were genotype 1, two were genotype 2, two were genotype 3, and one was genotype 4. Only two RCC patients had undergone previous IFN/ribavirin antiviral therapy for the treatment of their HCV infection, each without a virologic response. The estimated mean duration of HCV disease in our cohort was 15 years, with most patients having disease for >20 years. There was no substantial difference in body mass index between the HCV-positive RCC patients (mean, 28.6; range, 18.2-39.5) and the HCV-negative RCC patients (mean, 31.1; range, 19.4-53.6).

Abdominal imaging

Among the entire study population, 49% of HCV-negative patients had imaging studies done on ≥1 occa-

sions, whereas 80% of HCV-positive patients did. However, of patients with underlying kidney disease, the proportion that underwent imaging at least once was equivalent: 93% of HCV-negative patients and 92% of viremic patients.

Renal cell carcinoma

RCC was diagnosed in 0.6% (17 of 3,057) of HCV-positive patients versus 0.3% (177 of 64,006) of HCV-negative patients (Table 2). The diagnosis of RCC was established histologically in all except seven patients (all in the HCV-negative cohort) whose diagnoses were derived from computed tomographic (*n* = 4) or magnetic resonance (*n* = 3) imaging studies showing renal masses highly suspicious or otherwise consistent with the diagnosis. The mean age at RCC diagnosis was much younger in HCV-positive individuals (54 versus 63 y; $P < 0.001$).

To explore the possibility of screening bias in detecting RCC, we examined whether screened patients presented with smaller-sized tumors. The mean tumor size at presentation was 3.8 cm among HCV-positive patients versus 4.8 cm among HCV-negative patients ($t = 1.102$; $P = 0.272$). Among RCC patients, the mean tumor size at presentation was 4.8 cm for those who underwent imaging, similar to the mean of 4.9 cm for those who did not ($t = 0.092$; $P = 0.926$).

For the Cox regression and Kaplan-Meier analyses, we included only patients with >1 encounter with the healthcare system: 3,005 HCV-positive patients (16 with RCC) and 63,228 HCV-negative patients (174 with RCC). Among these patients, the mean length of observation time from HCV testing to diagnosis of RCC, death, or last visit to the healthcare system was 6.6 years for HCV-positive patients and 7.3 years for HCV-negative patients.

In the Cox proportional hazards modeling, the univariate hazard ratio for RCC among HCV patients was 2.20 (95% confidence interval, 1.32-3.67; $P = 0.0025$; Table 3). In the multivariate model that included age, African-American race, male gender, and CKD, the overall hazard ratio for RCC among HCV patients was 1.77 (95% confidence interval, 1.05-2.98; $P = 0.0313$). Each tested variable was a statistically significant predictor of kidney

Table 3. Cox regression analysis for predicting RCC

	Univariate		Multivariate	
	HR (95% CI)	*P*	HR (95% CI)	*P*
HCV positive	2.20 (1.32, 3.67)	0.0025	1.77 (1.05, 2.98)	0.0313
Age	1.04 (1.04, 1.06)	0.0001	1.03 (1.02, 1.04)	0.0001
African-American race	1.73 (1.30, 2.31)	0.0002	1.40 (1.04, 1.90)	0.0271
Gender: male vs female	2.67 (1.96, 3.64)	0.0001	2.41 (1.77, 3.28)	0.0001
Chronic kidney disease	7.76 (5.83, 10.32)	0.0001	4.39 (3.20, 6.03)	0.0001

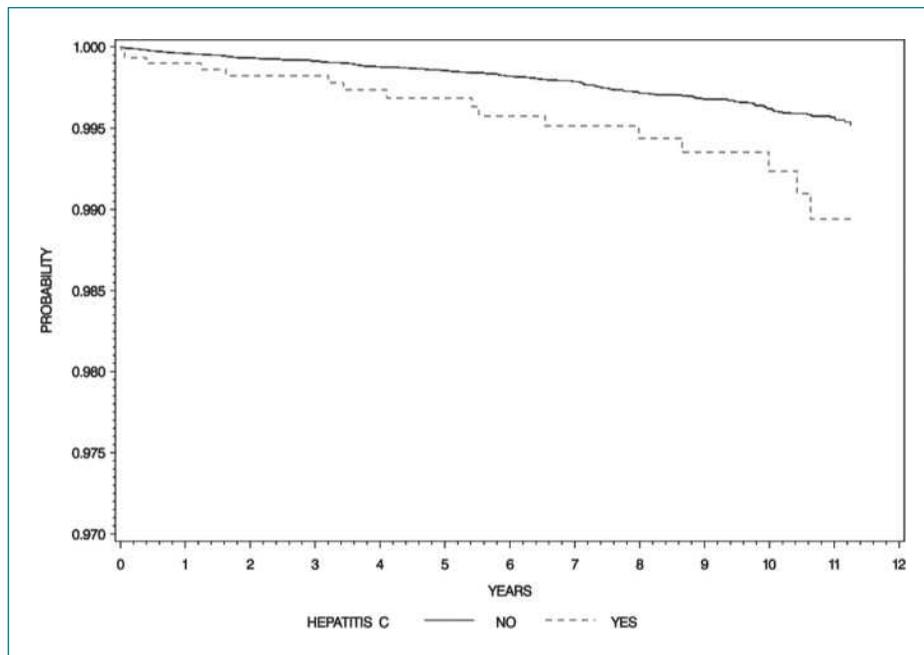Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval.

Figure 2. Cumulative risk for renal cell carcinoma among patients with chronic hepatitis C. Kaplan-Meier curve for freedom from renal cell carcinoma by hepatitis C status (log-rank $P = 0.002$).

cancer outcome, both in univariate and multivariate tests. With the Cox multiple regression analysis, HCV positivity conferred a 77% increased risk of developing RCC.

The Kaplan-Meier curves for freedom from kidney cancer indicated that patients in the HCV-positive group had a statistically significant increased risk for RCC (log-rank $P = 0.002$; Fig. 2).

When we did Cox regression analysis and Kaplan-Meier plots including only the patients without kidney disease, the results were similar to the analysis that included the CKD patients. In this analysis (Table 4), hepatitis C infection remained a predictor of kidney cancer, now with a multivariate hazard ratio of 2.02. In a separate Kaplan-Meier plot that excluded all CKD patients (Fig. 3), the log-rank P-value of 0.007 indicates the detection of a statistically significant increased risk for RCC.

Discussion

This analysis of >67,000 patients is the first report to show that chronic infection with HCV is associated with a higher incidence of RCC. The average age of HCV-positive patients with RCC was significantly younger than that of HCV-negative patients with RCC, a cancer that generally affects older individuals (15). Our findings validate previously published reports (10, 16) suggesting that older age and African-American race are independent risk factors for RCC. Our findings thus corroborate our own clinical observations and seropositivity data, as well as frequent anecdotal reports in the literature that have strongly suggested an association between chronic HCV infection and RCC (11-14, 17).

In addition to the incidence of RCC being higher among HCV (confirmed viremic) patients, the measured 4.3% HCV seroprevalence (anti-HCV positivity rate) in our RCC patients is likewise higher than the overall seroprevalence of HCV in the United States, which is ~1.6% (18). Our study population consisted of patients who underwent HCV testing as part of their overall medical care, and for some patients, such as those undergoing dialysis, this testing was done because of their perceived increased risk for HCV. Nevertheless, our reported HCV

Table 4. Cox regression analysis for predicting RCC in absence of concomitant kidney disease

	Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
HCV positive	2.49 (1.25, 4.93)	0.0091	2.02 (1.01, 4.06)	0.0481
Age	1.05 (1.03, 1.06)	0.0001	1.05 (1.04, 1.07)	0.0001
African-American race	1.21 (0.82, 1.79)	0.3342	1.51 (1.01, 2.24)	0.0450
Gender: male vs female	2.50 (1.65, 3.79)	0.0001	2.36 (1.56, 3.59)	0.0001

Figure 3. Cumulative risk for renal cell carcinoma among patients with chronic hepatitis C but without kidney disease. Kaplan-Meier curve for freedom from renal cell carcinoma by hepatitis C status excluding kidney disease patients (log-rank $P = 0.007$).
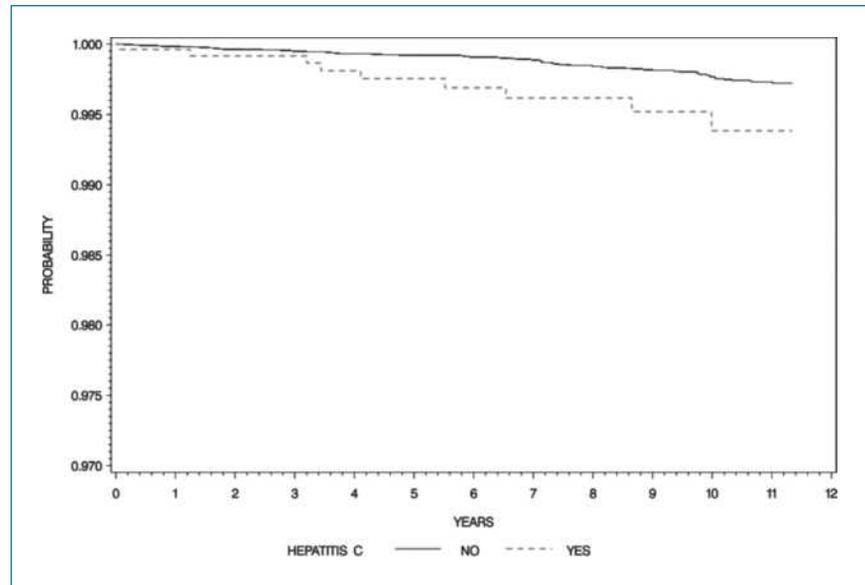
seroprevalence among RCC patients is higher than the HCV seroprevalence among breast, colorectal, or prostate cancers, and the rates of HCV that we observed in these other malignancies are generally consistent with the reported U.S. HCV seroprevalence rates. Although specific HCV seroprevalence for our geographic region is not available, it is undoubtedly higher than for the rest of the United States (19), owing to a high number of injection drug users (an estimated 35,000) in Detroit. No study to date has looked at an association between injection drug use and RCC.

The inherent screening bias of the present administrative cohort analysis may be interpreted as advantageous. Presumably, the subjects tested for anti-HCV in this study represented those at increased risk for HCV; thus, the negative control cohort did not reflect the general healthy population at large but rather a population defined by its documented absence of viral hepatitis positivity. This population is unlikely to have an under-representation of recognized RCC risk factors (smoking, obesity, hypertension, etc.) compared with the general population. HCV patients infected through injection drug use are more likely to have smoked tobacco than those infected through another manner. To explore the possibility that infection with HCV represented a surrogate marker of the recognized tobacco risk factor, we looked at risk of lung cancer in this cohort and found no increase compared with uninfected controls.

We excluded 5,424 patients of ~8,500 anti-HCV–positive individuals because they lacked confirmation of viremia. These excluded patients consisted not only of those who were presumed either false seropositive or spontaneously cleared (anti-HCV positive and HCV RNA negative) but also individuals who tested intermittently anti-HCV negative (transient positivity). Also excluded were anti-HCV patients who were likely viremic

but for whom no molecular confirmation existed. Thus, we included only 16 viremic cancer patients in the Cox regression model (1 patient was excluded for having only one encounter with the healthcare system). In a separate analysis that did not exclude the 5,424 patients and included only seropositive RCC patients, HCV infection remained a significant RCC predictive variable (data not shown).

The strengths of our analysis include having a very large, ethnically diverse, and well-defined cohort of individuals with ongoing contact with an integrated healthcare system, and serologic and virologic documentation of HCV infection status. In addition, in all but seven cases we established the diagnoses of kidney cancer by reviewing pathology reports, and hepatitis C diagnoses were made on the basis of confirmed viremia rather than ICD-9-CM codes. Having a control cohort of confirmed anti-HCV–negative subjects would likely be difficult in a matched–control cohort analysis because confirmation of viral negativity in the control RCC subjects would be an obstacle in most settings.

This study has potential limitations in addition to lack of systematic tobacco histories. Possible referral bias inherent in a hepatologic and urologic tertiary medical center is another consideration. In 96.4% of the subjects, we established the presence of RCC by pathology confirmation following surgery or at autopsy. Some patients with renal masses, such as older individuals or those with co-morbid conditions, may not undergo surgical resection and instead may undergo active surveillance or ablation, in which case pathologic confirmation of cancer is not possible. Nevertheless, our cancer registry recorded the diagnosis of RCC if renal cancer was highly suspected by the radiologist, which lessens the possibility that conservatively managed RCC patients were excluded. Imaging screening bias may have occurred, because more HCV-positive patients underwent abdominal imaging

than nonviremic patients. This difference, however, was not observed among patients with CKD. Moreover, we found no difference in size of tumor at presentation between screened versus unscreened patients, or between HCV-positive versus HCV-negative patients, mitigating against the notion that HCV patients presented with incidental tumors or that screening bias affected the observed relationship. Our analysis does not, however, completely exclude the possibility of bias due to different rates of imaging.

HCV-seropositive subjects manifested demographic differences compared with HCV-seronegative subjects, which might be expected to increase their risk of RCC. Whereas our statistical analyses adjusted for potential confounding by these factors, it is possible that residual confounding from unmeasured variables remains.

Finally, having disproportionate numbers of dialysis patients in the tested cohort represents a confounding variable. The potential over-representation of dialysis patients, who undergo routine hepatitis testing, likely contributed to the observation that CKD was a significant risk for RCC in our cohort. Historically, CKD has not been acknowledged as a strong RCC risk, although more recent literature has in fact suggested such an association, which may or may not reflect an etiologic relationship (20, 21). Chronic HCV infection does increase the overall risk for the development of renal disease in general (22), however; whereas it is probable that this phenomenon affected the CKD incidence in the current cohort, chronic HCV infection, independent of CKD, remained an independent RCC risk in multivariate regression modeling. Moreover, in a separate model that excluded all CKD patients, HCV remained an independent predictor of RCC.

HCV has purported oncogenic potential in the liver and lymphatic system, and HCV RNA and core protein have been isolated in kidney glomerular and tubular structures (3). The cell of origin of RCC depends on the histologic subtype. The most common subtype is clear-cell RCC, which originates from proximal convoluted tubule cells. Glomerular cells are not a typical origin of RCC; thus, infection of tubular rather than glomerular cells is more likely to be involved in the process of oncogenesis. In transgenic mice, constitutive expression of HCV core protein can induce hepatocellular carcinoma (23). There is evidence that activation of peroxisome proliferator-activated receptor α, which regulates transcription of genes encoding fatty acid–metabolizing enzymes, is essential for the induction of hepatocellular carcinoma by HCV core protein (24). The precise mechan-

isms by which HCV leads to hepatocellular carcinoma, however, are not clear at this time nor is it known whether similar mechanisms could be implicated in RCC.

It has been noted that IFN-α, which is indicated for treatment of chronic HCV infection, is also used to help stabilize advanced RCC (11, 25). In addition, there is evidence that HCV patients who achieve viral eradication following IFN therapy have a lower incidence of malignant lymphoma (26). It is possible that suppression of HCV replication has a protective effect against certain oncogenic processes.

In summary, data from a large cohort study suggest that chronic infection with HCV confers an increased and independent risk for developing RCC, one of the few cancers with rising global incidence. The results of this study would suggest a more careful surveillance of newly diagnosed RCCs for the presence of HCV infection. It is premature to recommend more comprehensive screening of HCV-positive patients for this relatively uncommon neoplasm. However, a heightened awareness of an increased kidney cancer risk should dictate more careful follow-up of incidental renal defects when detected on imaging procedures in patients with chronic hepatitis C. Additional studies are required to confirm these findings and to explore potential mechanisms of oncogenesis. The study population and demographics of such cohorts, however, are subject to the recognized epidemiology of RCC, which include older age and higher proportions of individuals of African descent.

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