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ORIGINAL ARTICLE

Chronic Hepatitis C Infection as a Risk Factor for Renal Cell Carcinoma

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Abstract
Background Chronic hepatitis C virus (HCV) infection causes cirrhosis and hepatocellular carcinoma but is also etiologically linked to several extrahepatic medical conditions including renal disorders. HCV is also associated with extrahepatic malignancies and may be oncogenic. Whether HCV confers an increased risk of renal cell carcinoma (RCC) remains controversial.
Aims Prospectively determine whether chronic HCV is associated with an increased risk of RCC.
Methods At an integrated medical center in Detroit, Michigan, adult patients with suspected RCC or newly diagnosed colon cancer (controls) were screened for hepatitis C antibody (HCAB) and HCV RNA. Renal or colon cancers were confirmed histologically. The proportion of patients with HCAB and HCV RNA in each group was compared, and risk factors for renal cell carcinoma were determined by multivariable logistic regression analysis.
Results RCC patients had a higher rate of HCAB positivity (11/140, 8 %) than colon cancer patients (1/100, 1 %) ($p < 0.01$). Of the HCAB-positive patients, 9/11 RCC and 0/1 controls had detectable HCV RNA. HCV RNA positivity was a significant risk factor for RCC (OR 24.20; 95 % CL 2.4, >999.9; $p = 0.043$). Additionally, viremic RCC patients were significantly younger than RCC patients who were HCV RNA negative ($p = 0.013$).
Conclusions Patients with chronic HCV are at heightened risk of RCC.

Keywords Hepatitis C · Renal cell carcinoma · Extrahepatic manifestations · Prospective study

Introduction

Among the estimated 150 million individuals infected worldwide with HCV, a significant proportion will develop hepatic manifestations including chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC). Additionally, chronic HCV infection has oncogenic and lymphoproliferative properties and is associated non-Hodgkin lymphoma and perhaps myeloma [1, 2]. Chronic HCV infection increases the likelihood of renal disease, and the prevalence of chronic kidney disease among infected patients is up to 40 % higher compared with uninfected patients [3].

Kidney cancer accounts for about 2 % of all new cancer cases worldwide, with the majority (85 %) of parenchymal origin (RCC). The main risk factors for RCCs are cigarette smoking, obesity, hypertension, family history, and the inherited forms of the disease. For the last three decades,

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the incidence of RCC has increased steadily each year in Europe and the USA, and this rising incidence is not accounted for entirely by improved imaging modalities [4].

HCV RNA and HCV core protein have been detected in glomeruli and tubular structures by immunohistochemistry, in situ hybridization, and laser capture microdissection in different renal diseases [5]. Early reports and case series linked HCV and RCC in a variety of clinical scenarios including patients with uncomplicated HCV infection, pre-liver transplant, HCC, and hemodialysis [6–9]. In our previous retrospective cohort study at a large and ethnically diverse medical center, we found that the incidence of RCC was doubled in HCV-positive patients and that these cancer patients were significantly younger when compared with their HCV-negative counterparts [10]. The possible link between chronic HCV infection and RCC has been investigated in two subsequent retrospective studies with conflicting results [11, 12]. The aim of the present study was to prospectively determine whether the risk of RCC is elevated in chronic HCV infection.

Methods

Study Population and Ethical Procedures

Participants were adults aged 18 years and older at the Henry Ford Health System in Detroit, Michigan (ClinicalTrials.gov: NCT01405183). The study group consisted of consecutive patients at the urology clinic who were scheduled for a partial or total nephrectomy or cryoablation with biopsy because of axial imaging indicating the possibility of RCC. Patients were recruited for the study either preoperatively or during a follow-up visit within 1 month after surgery.

The control group consisted of consecutive individuals newly diagnosed with colon cancer. The control group was recruited simultaneously and from the same health care system. Patients were recruited for the study either preoperatively or during a follow-up visit within 1 month after surgery. The colon cancer subjects had confirmatory histopathology (<6 months) or had very strong suspicion of colorectal cancer (high-grade dysplasia in an unresectable polyp or obstructive malignant-appearing colonic lesion imaged during endoscopy) and were scheduled for hemi- or total colectomy. Records from the gastroenterology tumor board meeting were also reviewed to capture additional patients from within the health care system.

More than 90 % of RCC patients and controls were enrolled preoperatively.

Study inclusion required patients to have RCC or colon cancer confirmed by histopathology. Patients with colon cancer related to inflammatory bowel disease were excluded.

From January 2011 through August 2013, 374 patients were approached about study participation, and 105 patients declined consent (64 colon cancer patients and 41 RCC patients); 29 patients were screen failures.

All patients provided written informed consent. The study protocol was approved by a local institutional review board. The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

Assessments

Patient Questionnaire

All patients completed a questionnaire that captured information regarding demographics, risk factors for RCC and HCV, chronic medical conditions, and personal and family history of cancer.

HCV Serology and Molecular Diagnostics

The presence of hepatitis C antibody (HCAB) was detected by using the ADVIA Centaur Immunoassay System (Siemens Healthcare Diagnostics, Tarrytown, New York). HCV RNA was evaluated by using the Roche COBAS AmpliPrep/COBAS TaqMan HCV Test (Roche Diagnostics, Indianapolis, Indiana). Patients who had a positive HCAB and positive HCV RNA results were asked to have a second blood draw to determine HCV genotype (rtPCR amplification of the 5′ untranslated region of the HCV genome followed by reverse hybridization by using the LINEAR ARRAY Hepatitis C Virus Genotyping Test for use with the AMPLICOR® and COBAS® AMPLICOR HCV Test, v2.0, Roche Molecular Systems, Inc. or the Abbott Real*Time* HCV genotype II Assay [Abbott Laboratories, Abbott Park, Illinois]).

Patients with discordant results (positive HCV RNA and negative HCAB or vice versa) were retested for HCV RNA whenever possible. If a subject was previously known to have chronic hepatitis C infection, the HCAB, HCV RNA, and HCV genotype assays were performed simultaneously.

Sample Size Calculation

Using a total of 140 RCC patients (study group) and 100 colon cancer patients (control group) along with a standard two-sided alpha level of 0.05, this study had a *t* test power of 0.80 to detect an underlying effect size of 0.37 (i.e., a mean group difference which is 0.37 times the size of the corresponding standard deviation).

Statistics

Comparison of continuous baseline variables was done by *T* test. Multivariable logistic regression was performed to compare the proportions of HCV RNA-positive patients in the RCC and colon cancer groups. To correct for bias from quasi-complete separation of the HCV RNA variable, the Firth method of penalized maximum likelihood was used. This method can be used when a 2×2 table that represents the relationship between the exposure and the response variable has one cell with a zero frequency, as in the case for our study, with HCV viremic status in our colon cancer patients.

Results

A total of 140 RCC and 100 colon cancer patients were enrolled. The RCC and colon cancer groups did not differ on the basis of gender, race, tobacco use, alcohol abuse, illicit drug use, or the presence of cirrhosis (Table 1). RCC patients were significantly younger than colon cancer patients and had higher rates of hypertension, chronic kidney disease, and renal replacement therapy. In the RCC group, 11 patients were HCAB positive, and nine of them were HCV RNA positive. Of the patients with negative HCV RNA, one had been successfully treated with antivirals and the other had a negative RIBA test. Three additional patients were HCAB negative but had detectable (<41 IU/ml) or very low levels (61 IU/ml) of HCV RNA. One patient was retested and found to be aviremic. The two remaining patients could not be retested and were presumed to have false-positive results. Seven out of the nine HCV RNA-positive RCC patients were HCV genotype 1, and the remaining two individuals were genotype 2 and 3, respectively.

All RCC patients with chronic HCV infection were aware of their viral infection prior to the diagnosis of RCC. The mean duration of viremia was 31.6 years. Two out of the nine viremic RCC patients had pre-surgical liver biopsies revealing minimal fibrosis (Ishak 1–2). The remaining seven patients had cross-sectional imaging that showed evidence of cirrhosis in three cases.

The mean age of RCC patients with viremia (56.7 years) was lower relative to aviremic patients (61.8 years, $p = 0.013$). Three of these patients were suspected of having RCC as a result of cross-sectional imaging obtained during screening for hepatocellular carcinoma. Two patients, both HCAB and HCV RNA positive, had end-stage renal disease and were on long-term dialysis. The two RCC patients who were HCAB positive but HCV RNA negative (false positive) were not on long-term renal replacement therapy. Ten additional RCC patients were on hemodialysis, but none of them was HCAB or HCV RNA positive.

No colon cancer patients had chronic HCV infection. One patient had positive HCAB but was HCV RNA negative. Two additional patients had negative HCAB but

Table 1 Patient characteristics

	RCC ($n = 140$)	Controls ($n = 100$)	p value
Male gender, *n* (%)	85 (60.7)	59 (59.0)	0.789
Race, *n* (%)			
Non-African-American	86 (61.4)	49 (49.0)	0.056
African-American	54 (38.6)	51 (51.0)	
Age, mean years	61.5	65.7	0.004
BMI	30.1	29.1	0.334
Tobacco use, *n* (%)			
History	80 (57.1)	62 (62.0)	0.450
Current	15 (10.7)	11 (11.0)	0.486
Alcohol abuse, *n* (%)			
History	14 (10.0)	16 (16.0)	0.166
Current	1 (0.7)	2 (2.0)	0.378
Illicit drug use, *n* (%)	13 (9.3)	2 (2.0)	0.021
Hypertension, *n* (%)	92 (65.7)	49 (49.0)	0.010
Chronic kidney disease, *n* (%)	19 (13.6)	3 (3.0)	0.006
Dialysis, *n* (%)	12 (8.6)	1 (1.0)	0.011
Cirrhosis, *n* (%)	4 (2.9)	2 (2.0)	1.000
Family history kidney cancer, *n* (%)	10 (7.1)	4 (4.0)	0.306
Hepatitis C status, *n* (%)			
Hepatitis C antibody positive	11 (7.9)	1 (1.0)	0.016
HCV RNA positive	9	0	0.012

BMI body mass index, *HCV* hepatitis C virus, *RCC* renal cell carcinoma

detectable (<41 IU/ml) HCV RNA, which was presumed to represent falsely positive molecular assay results.

In the multivariable logistic regression analysis, being HCV RNA positive ($p = 0.043$) was a significant risk factor for RCC (Table 2). African-American race, the presence of hypertension, and the presence of chronic kidney disease were also associated with increased risk of RCC.

Discussion

Recent reports have shown that HCV is associated not only with increased mortality from hepatic disease and malignancy but also with a number of extrahepatic malignancies including genitourinary cancers [13, 14]. In our previous retrospective cohort analysis, we showed that HCV viremic patients had double the risk of RCC compared with anti-HCV-negative patients [10]. Such retrospective analyses, however, are limited by potential ascertainment biases at tertiary medical centers.

To our knowledge, this is the first prospective study to indicate that patients with HCV are at heightened risk of RCC as compared with our control cohort, and these results confirm our previous retrospective observations [10]. We chose colon cancer patients as controls because this malignancy has not been previously associated with HCV infection and because of our ability to approach these patients in our Gastroenterology Unit.

Although discordant from results of retrospective studies in Sweden and Turkey [11, 12], our findings are likewise consistent with results from a recent analysis of persons residing in the state of Washington. In 2013, Macleod et al. [15] identified self-reported viral hepatitis as an independent risk factor for RCC, although this report did not include actual virologic testing to discern type of viral hepatitis. A population-based cohort study in Denmark also indicated that HCV-infected persons have an increased risk of not only HCC but also non-Hodgkin lymphoma and cancers of the pancreas, lungs, kidneys, and oropharyngeal region [16]. Additionally, HCV infection in the USA has recently been associated with elevated rates of death from genitourinary disease [17] and from extrahepatic malignancy such as non-Hodgkin lymphoma and oral cavity cancer [14].

It is unclear whether the association between HCV infection and RCC is related to lifestyle factors in the HCV-infected population, mechanisms related to viral infection, or both. In this analysis, neither tobacco use nor alcohol abuse was associated with increased risk of RCC, suggesting that the link between HCV and RCC is not directly attributable to lifestyle factors.

In our study, 11 RCC patients had a positive HCAB, but only nine (81 %) were viremic, which is consistent with prior prevalence US studies [18, 19]. The prevalence of HCAB positivity in hemodialysis patients is higher than the general population (7.8–13.5 %) [20, 21]. In our study, two out of the nine viremic RCC patients were on long-term dialysis. However, 10 other RCC patients who were on hemodialysis were HCAB and HCV RNA negative, suggesting that hemodialysis was not a confounding factor for hepatitis C in this study.

In HCV-mediated chronic kidney disease, HCV RNA and core protein have been isolated in kidney glomerular and tubular structures [5], although it is not clear whether their presence would mediate oncogenesis. Wiwanitkit recently postulated the biologic plausibility of this particular oncogenic association that implicates the NY-REN-54, which is a ubiquitin-related protein common to both RCC and HCV [22].

Table 2 Multivariable logistic regression analysis of renal cell carcinoma risk factors

	Odds ratio (95 % confidence limits)	*p* value
HCV RNA	24.20 (2.4, >999.9)	0.043
Male	0.52 (0.5, 1.7)	0.85
African-American	0.25 (0.3, 0.8)	0.012
Age	0.96 (0.9, 1.0)	0.011
BMI	0.96 (0.7, 1.4)	0.81
Smoking	0.85 (0.5, 1.5)	0.58
Alcohol abuse	0.41 (0.2, 1.0)	0.070
Hypertension	2.48 (1.3, 4.9)	0.008
Diabetes mellitus	0.64 (0.3, 1.3)	0.20
Dyslipidemia	1.58 (0.9, 2.9)	0.16
Coronary artery disease	0.93 (0.4, 2.2)	0.87
Congestive heart failure	0.75 (0.2, 3.0)	0.68
Chronic kidney disease	3.71 (1.2, 15.1)	0.042
Cirrhosis	0.79 (0.2, 9.4)	0.79

Firth's penalized maximum likelihood method and profile likelihood confidence intervals

BMI body mass index, *HCV* hepatitis C virus

The mean age of RCC patients was younger than that of colon cancer patients, which is consistent with epidemiologic surveillance data [23, 24]. In addition, the mean age of RCC patients with HCV (56.7 years) was lower than that of aviremic patients (61.8 years) and of RCC patients in a nationwide surveillance program (63.5 years) [23]. In our previous retrospective analysis, the average age of HCV-positive patients with RCC was likewise significantly younger than that of HCV-negative patients with RCC [10]. The finding that HCV-positive RCC patients are significantly younger than HCV-negative RCC patients is similarly consistent with the hypothesis that HCV is potentially linked to RCC development, and implicates RCC as one of the emerging extrahepatic malignancies associated with the hepatitis C virus.

A limitation of this study is that there is a potential for screening bias in patients with suspected kidney cancer versus colon cancer. However, such bias is expected to be small and it is noted that only three of nine patients with HCV had their RCC diagnosed as a result of imaging screening for HCC. Additionally, our study population was relatively small, but RCC is a relatively uncommon cancer; we achieved a recruitment rate of approximately 70 % during a 2.6-year enrollment period.

In conclusion, this analysis suggests that chronic infection with HCV is associated with having RCC. This study adds to previous literature showing the relationship between HCV and extrahepatic malignancies. Future studies should identify potential mechanisms by which chronic HCV infection may facilitate either the development or the progression of RCC.

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Conflict of interest None.

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