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Risk of kidney cancer and chronic kidney disease in relation to hepatitis C virus infection: a nationwide register-based cohort study in Sweden

Jonathan N Hofmann¹, Anna Törner², Wong-Ho Chow¹, Weimin Ye³, Mark P Purdue¹, and Ann-Sofi Duberg⁴

¹Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD

²Department of Epidemiology, Swedish Institute for Infectious Disease Control, Solna, Sweden

³Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden

⁴Department of Infectious Diseases, Örebro University Hospital, Örebro, Sweden

Abstract

Chronic hepatitis C virus (HCV) infection is an established cause of liver cancer, and recent studies have suggested a link with kidney cancer. The aim of this study was to evaluate risk of kidney cancer in relation to HCV infection in a nationwide registry-based study of Swedish residents diagnosed with HCV between 1990 and 2006. A total of 43,000 patients with chronic HCV infection were included, and the mean follow-up time was 9.3 years. Observed kidney cancer incidence and mortality in the cohort were compared with expected values based on the age- and sex-adjusted rates in the general population. Risk of hospitalization for other chronic kidney disease was also evaluated using Cox proportional hazards regression. No association between HCV infection and risk of kidney cancer was observed [standardized incidence ratio with one-year lag = 1.2; 95% confidence interval (CI) 0.8–1.7]. Risk of hospitalization for non-cancer kidney disease was significantly elevated in the HCV cohort, with significantly stronger associations observed among women than among men [hazard ratio = 5.8 (95% CI 4.2–7.9) and 3.9 (95% CI 3.2–4.8) for women and men, respectively]. Results of this study do not support the hypothesis that chronic HCV infection confers an increased risk of kidney cancer. However, we did find an association between HCV infection and chronic kidney disease, particularly among women. Given inconsistent findings in the literature, it is premature to consider HCV infection to be a risk factor for kidney cancer.

Keywords

chronic hepatitis C virus infection; renal cell carcinoma; kidney cancer; cancer registry; chronic kidney disease

Correspondence to: Jonathan N Hofmann, PhD, MPH, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd, EPS 8109, MSC 7240, Bethesda, MD 20892-7240, Tel: 301-402-2605, Fax: 301-402-1819, hofmannjn@mail.nih.gov.

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Introduction

Approximately 170 million people throughout the world are chronically infected with the hepatitis C virus (HCV) [1, 2]. Chronic HCV infection has been recognized as a major cause of liver cancer [3] and has been consistently associated with increased risk of non-Hodgkin lymphoma [4, 5].

HCV infection is also associated with chronic renal disease [6, 7], and HCV-RNA and HCV proteins have been isolated in kidney tissue from HCV-infected patients with various forms of glomerulonephritis [8, 9]. In a nationwide register-based cohort of all diagnosed HCV-infected residents of Sweden, risk of death due to kidney cancer was significantly elevated [10]. A more recent epidemiologic study by Gordon and colleagues reported increased incidence of kidney cancer among HCV-infected individuals [11].

To follow up on previous findings of increased kidney cancer mortality in the cohort of HCV-infected residents of Sweden, we conducted an analysis of kidney cancer incidence in this population. Since the previous mortality study, an additional 7,164 HCV-infected subjects were added to the cohort and follow-up was extended through 2008, thus almost doubling the total observation time to include over 400,000 person-years. As a secondary analysis, we also evaluated risk of hospitalization for chronic kidney disease in relation to HCV infection.

Materials and Methods

Study population

Enumeration of the HCV cohort has been described previously [12]. Briefly, records for all residents of Sweden who were notified of HCV infection between 1990 and 2006 were extracted from the national surveillance database at the Swedish Institute for Infectious Disease Control (SMI). Both the diagnosing laboratory and clinician are required to report HCV infections to the SMI, and the SMI database includes information of epidemiologic interest such as date of HCV notification and suspected route of transmission. The sensitivity of this reporting system is high (>98% in 2002 for notifiable infections studied thus far) [13]. Because unique personal identification numbers (available for all Swedish residents) were needed for linkage with other registers, HCV records without complete ID numbers (N = 623) were excluded from this analysis. Six additional subjects with conflicting data (e.g., deaths prior to HCV notification) were also excluded. After these exclusions, a total of 43,000 subjects remained in the HCV-infected cohort for this analysis.

To evaluate risk of chronic kidney disease other than cancer, we compared the HCV cohort with a non-HCV-infected cohort selected from the general population and matched on year of birth, sex, and county of residence in Sweden. Five subjects never diagnosed with HCV infection were matched to each HCV-infected subject, resulting in a cohort of 215,000 subjects not diagnosed with HCV. To avoid selection bias, subjects were excluded from these analyses if they had ever been hospitalized with kidney disease as the principal diagnosis from 1969 until one year after HCV notification or the corresponding reference date for non-HCV-infected subjects (codes ICD-8: 189, 580–584; ICD-9: 189, 580–589, 593; ICD-10: C64–C66, C68, N00–N08, N17–N19, N25–N28). Subjects who were hospitalized for any condition in the year prior to HCV notification were also excluded, leaving 25,412 HCV-infected subjects and 198,124 subjects never diagnosed with HCV in these analyses.

Linkage to other registers

Records from the SMI register were linked with several other national registers for this study. The Swedish Population register maintained by Statistics Sweden was used to identify the matched non-infected cohort and to obtain information on dates of immigration, emigration, or death. The National Board of Health and Welfare added information from the national Cancer, Cause of Death and Hospital Discharge registers. Incident cases of kidney cancer were identified through the Cancer register; case ascertainment in this register is very high (95% of detected cancers), and nearly all (99%) reported cases are histologically or cytologically confirmed [14]. Cancer diagnoses were coded using the seventh revision of the International Classification of Diseases (ICD-7). We extracted information on incident kidney cancer cases (excluding cases of renal pelvis cancer) diagnosed between 1990 and 2008 (ICD-7 codes 180.0 and 180.9). Histologic confirmation was available for all of the kidney cancer cases in the HCV cohort. One kidney tumor was benign and excluded from these analyses. The 25 patients with kidney cancer diagnosed prior to HCV notification were excluded. Subjects who were diagnosed with other types of cancer were not excluded from the study cohort or from the population incidence rates. Only one of the kidney cancer cases in the HCV cohort had been previously diagnosed with another cancer. We also extracted information from the Cause of Death register on kidney cancer mortality (listed as the underlying cause of death) between 1990 and 2007, the last year for which these data were available (1990–1997, ICD-9 codes 189.0, 189.9; 1998–2007, ICD-10 code C64).

Data on hospitalization discharge diagnoses were extracted from the Hospital Discharge register, which started in 1964 and since 1987 has covered all inpatient care in Sweden. Secondary analyses were performed to evaluate risk of inpatient hospitalization for treatment of the following chronic kidney diseases from 1990–2008: 1) glomerular diseases (ICD-9 codes 580–583, ICD-10 codes N00–N08); 2) renal failure (ICD-9 codes 584–586, ICD-10 codes N17–N19); and 3) other kidney diseases (ICD-9 codes 587–589 and 593, ICD-10 codes N25–N28). Events were defined as the first hospitalization per subject for which each of the aforementioned conditions was listed as the principal diagnosis code.

Statistical analysis

The kidney cancer risk in the HCV cohort was expressed as standardized incidence ratios (SIRs) calculated by dividing the number of observed kidney cancers by the expected number. To calculate the expected number of cancers, we used sex-, age-, and calendar year-specific incidence rates from the general population in Sweden multiplied by the number of person-years within each stratum in the HCV cohort. Subjects were followed from HCV notification until the time of kidney cancer diagnosis, death, emigration (available through 2007 only), or 31 December 2008, whichever came first (total of 400,196 person-years). To evaluate potential effects of selection bias on risk estimates, analyses were performed using various lag periods after HCV notification (none up to two years) for the start of follow-up and calculation of person-years. Stratified analyses were performed by sex, estimated duration of HCV infection, and year of birth. Estimated duration of HCV infection was characterized using a previously developed model based on age, suspected route of transmission, and the epidemiology of HCV transmission in Sweden [15]. We also evaluated the relative risk of death due to kidney cancer in relation to HCV infection by calculating standardized mortality ratios (SMRs) using the same methods as described above. Exact 95% confidence intervals (CIs) for the SIRs and SMRs were calculated assuming a Poisson distribution for the observed number of cases and deaths.

For the analyses of chronic kidney disease in relation to HCV infection, we used Cox proportional hazards regression to evaluate time until first hospitalization for chronic kidney disease in the HCV cohort relative to the non-HCV-infected cohort described above.

Follow-up began at one year after HCV notification (or the corresponding date for non-HCV-infected subjects). The Cox regression models included terms for HCV status, age, sex, and interaction between HCV status and sex. Plots of the hazard functions were evaluated to confirm that the proportional hazards assumption was appropriate. Analyses were repeated after excluding 2,584 HCV-infected subjects for whom the suspected route of HCV transmission was through transfusion of blood or blood products or nosocomial infection to assess potential bias due to reverse causation (i.e., HCV infection resulting from treatment for chronic kidney disease).

Statistical analyses were performed using SAS software, V.9.1 (SAS Institute, Cary, NC, USA). Results were considered to be statistically significant if p-values were less than 0.05.

Ethics and confidentiality

All study procedures were approved by the Regional Ethical Review Board in Stockholm, Sweden. After performing the record linkages, the personal identification numbers were deleted prior to analysis to ensure confidentiality of the dataset.

Results

Demographic and other characteristics of HCV-infected subjects are reported in Table 1. Most HCV-infected individuals were male (69%), and median age at HCV notification was 37.6 years. The most common suspected route of HCV transmission was intravenous drug use (58%).

Although we observed a slight increased incidence of kidney cancer among HCV-infected individuals overall, this association was reduced to an insignificant level with three-month and one-year lag periods (Table 2). Results were similar after restricting to adenocarcinomas only (SIR with a one-year lag period = 1.1; 95% CI 0.7–1.6; 26 observed cases in the HCV cohort). Stratified analyses showed minor differences by sex [SIR = 1.3 (95% CI 0.5–2.7) and 1.1 (95% CI 0.7–1.7) for women and men, respectively], and higher SIRs among subjects with an estimated duration of HCV infection of 20 years or less (SIR = 1.9; 95% CI 1.0–3.2) and among subjects born after 1959 (SIR = 1.7; 95% CI 0.6–3.7). We did not see an association between chronic HCV infection and kidney cancer mortality in an analysis with a two-year lag period (SMR = 1.2; 95% CI 0.6–2.2; 11 observed deaths in the HCV cohort).

Chronic HCV infection was associated with a significantly increased risk of hospitalization for other non-cancer kidney diseases (Table 3). Risk of all non-cancer kidney diseases differed significantly by sex ($P_{\text{interaction}} = 0.045$). Hazard ratios of 3.9 (95% CI 3.2–4.8) and 5.8 (95% CI 4.2–7.9) were observed among men and women, respectively. Among men, risk estimates ranged from 2.9 (95% CI 2.0–4.3) for glomerular diseases to 4.6 (95% CI 3.7–5.8) for renal failure. Among women, risk estimates ranged from 5.1 (95% CI 3.0–8.8) for glomerular diseases to 10.0 (95% CI 2.7–37.2) for other non-cancer kidney diseases. For all Cox regression analyses, we observed similar risk estimates after excluding individuals for whom the suspected route of HCV transmission was through transfusion of blood or blood products or nosocomial infection (data not shown).

Discussion

Overall, the findings of this study do not support the hypothesis that chronic HCV infection confers an increased risk of kidney cancer. After accounting for potential selection bias in lagged analyses, we did not observe associations between HCV infection and risk of kidney cancer.

The borderline significant increase in the SIR among individuals with shorter estimated duration of HCV infection but not among individuals with longer duration of HCV infection is contrary to expectations. This association may be driven by age-related differences in kidney cancer risk (age is highly correlated with estimated duration of HCV infection) or by frailty (i.e., greater susceptibility to kidney cancer development early in the course of infection, and thus decreasing risk for the remaining population with continued follow-up time). This finding may also be due to chance given the small number of expected cases in the stratum with shorter duration of HCV infection.

Associations between chronic HCV infection and kidney cancer have been reported previously, though results are somewhat inconsistent. A previous analysis of kidney cancer mortality among HCV-infected Swedish residents found a statistically significant increased risk compared to the general population [10]. In our more recent analysis of kidney cancer mortality, which had a longer lag period (2 years vs. 6 months) and included 7,164 additional HCV-infected subjects and four additional years of follow-up, we were unable to confirm this association. In another recent study of 3,057 HCV-infected patients identified through an administrative database from a large integrated healthcare system, Gordon et al. [11] reported a 77% increased risk of renal cell carcinoma incidence among HCV positive subjects relative to HCV negative subjects (N=17 cases of RCC among HCV-infected subjects). However, a community-based linkage study of 75,834 HCV-infected individuals in Australia found no association with kidney cancer incidence (N=18 cases of kidney cancer among HCV-infected subjects) [16].

Whereas we did not see an association between HCV infection status and risk of kidney cancer, we did observe strong, statistically significant associations with other chronic kidney disease. These findings are consistent with previous evidence of an increased risk of non-cancer kidney disease among HCV-infected individuals [6, 7, 17]. The consistency of these findings with results of prior studies of chronic renal disease other than cancer provides further support for the validity of these data.

We also observed stronger associations between HCV infection and non-cancer kidney disease among women than among men, which, to our knowledge, is a novel finding and should be confirmed in future studies. Although the HCV-related relative risk of kidney disease was greater for women than men, the background rates of kidney diseases were lower among women than among men in the reference population of Swedish residents, which is consistent with differences by sex in risk of end-stage renal disease observed in other populations [18]. Consequently, although these data indicate a stronger association between HCV infection and kidney disease among women than among men, the absolute risk of HCV-related kidney disease may not necessarily differ by sex. Differences in HCV-related kidney disease pathogenesis by sex could possibly be attributable to underlying biological characteristics [19], and further studies are needed to confirm these findings.

Strengths and Limitations

This population-based study utilized nationwide register data in Sweden between 1990 and 2008. With a total of 43,000 HCV-infected subjects and a mean follow-up of 9.3 years, this study is, to our knowledge, the largest investigation of HCV infection and kidney cancer to date in terms of person-years of observation. Another strength is the national system with personal identification numbers, which enables the linkage with other national registers and allows the assessment of individual risk over time. The nationwide communicable disease register at SMI has high sensitivity; among the 215,000 subjects in the reference population, there were only seven admissions (of 216,047) related to HCV infection that were not captured in the SMI database. The Cancer Registry also has high sensitivity, and all of the kidney cancer cases included in this analysis were histologically confirmed.

The possibility of selection bias is a limitation of this study. To address this limitation, we used the cumulative SIR method [20] and calculated SIRs with varying lag times (none up to two years). Exclusion of additional cases and person-time beyond a one-year lag period did not change the estimated SIR. Because treatment of end-stage renal disease may involve blood transfusions and hemodialysis, which are potential risk factors for HCV transmission, reverse causation bias was a potential concern in the analyses of hospitalizations for non-cancer kidney diseases. However, the impact of this type of bias on the reported results is likely minimal because all individuals with prior diagnoses of kidney diseases since 1969 were excluded from these analyses, and risk estimates were similar after excluding subjects for whom transfusion of blood/blood products or nosocomial infection was the suspected route of HCV transmission.

Finally, data on known risk factors for kidney cancer (e.g., smoking status, obesity) [21] were unavailable for adjustment. However, it is unlikely that the uncontrolled confounding would lead to both the null results for HCV infection and kidney cancer and a positive association for HCV infection and chronic kidney disease. The association with chronic kidney disease observed in our study is consistent with previous reports, which lends credence to our findings.

Conclusions

The results of this nationwide register-based study of residents of Sweden do not support the hypothesis that HCV-infected individuals are at an increased risk of developing kidney cancer. However, this study adds to the evidence that HCV infection confers an increased risk of non-cancer chronic kidney disease, particularly among women; further investigation of these apparent differences by sex is warranted.

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Table 1

Characteristics of the HCV-infected cohort*

	N (%) [†]
Number in the cohort	43,000
Deceased	8,519 (19.8)
Emigrated	1,467 (3.4)
Observation time in person years [‡]	400,196
Mean observation time, years [men; women]	9.3 [9.3; 9.3]
Male sex	29,698 (69.1)
Median age at HCV notification [men; women]	37.6 [37.7; 37.3]
Year of birth, median [range]	1959 [1898–2006]
Country of origin	
Nordic countries	38,178 (89.2)
Non-Nordic European countries	2,187 (5.1)
Other	2,450 (5.7)
Suspected route of HCV transmission	
Intravenous drug use	24,728 (57.5)
Blood/ blood products	2,448 (5.7)
Other	1,231 (2.9)
Unknown or missing	14,593 (33.9)
Ever hospitalized for selected obesity- or smoking-related conditions	
Diabetes	1,605 (3.7)
Chronic obstructive pulmonary disease	542 (1.3)
Lung cancer	259 (0.6)

* Includes individuals notified of HCV infection between 1990 and 2006

[†] Reported as frequencies (%) by category unless otherwise specified

[‡] Observation time was calculated from the date of HCV notification to kidney cancer diagnosis, death, emigration (available through 2007), or 31 December 2008

Table 2

Standardized incidence ratios for kidney cancer among 43,000 HCV-infected individuals

Characteristics	Observed	Expected*	SIR	95% CI
Lag period after HCV notification				
None	38	27.1	1.4	1.0–1.9
Three months	33	26.5	1.2	0.9–1.7
One year	29	24.9	1.2	0.8–1.7
Stratified analyses [†]				
Sex				
Male	22	19.6	1.1	0.7–1.7
Female	7	5.4	1.3	0.5–2.7
Estimated duration of HCV infection at time of notification				
≤20 years	13	6.9	1.9	1.0–3.2
> 20 years	16	18.0	0.9	0.5–1.4
Year of birth				
1959 or before	23	21.4	1.1	0.7–1.6
After 1959	6	3.6	1.7	0.6–3.7

* Calculated based on age, sex, and calendar year-specific kidney cancer incidence rates from the Swedish Cancer Registry

[†] Excluding cases and person-time during the first year after HCV notification

Table 3
Hazard ratios estimating risk of hospitalization for chronic kidney disease by HCV infection status*

Characteristics	Male			Female		
	N _{cases}	HR	95% CI	N _{cases}	HR	95% CI
<i>All non-cancer kidney diseases combined</i>						
No HCV infection	349	1.0	---	94	1.0	---
HCV infected	146	3.9	3.2–4.8	62	5.8	4.2–7.9
<i>Glomerular diseases</i>						
No HCV infection	104	1.0	---	34	1.0	---
HCV infected	35	2.9	2.0–4.3	22	5.1	3.0–8.8
<i>Renal failure</i>						
No HCV infection	245	1.0	---	59	1.0	---
HCV infected	115	4.6	3.7–5.8	46	7.2	4.9–10.6
<i>Other kidney diseases</i>						
No HCV infection	30	1.0	---	4	1.0	---
HCV infected	10	2.9	1.4–6.0	5	10.0	2.7–37.2

* Excludes subjects who were ever hospitalized with kidney disease from 1969 until one year after HCV notification (or the corresponding reference date for non-HCV-infected subjects) and subjects who were hospitalized for any condition in the year prior to HCV notification. A total of 25,412 HCV-infected subjects and 198,124 subjects never diagnosed with HCV were included in these analyses. Follow-up began at one year after HCV notification. Regression models included terms for HCV status, age, sex, and interaction between HCV status and sex.