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META-ANALYSIS

Hepatitis C infection and renal cell carcinoma: A systematic review and meta-analysis

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Abstract

AIM

To investigate the association between hepatitis C virus (HCV) infection and risk of renal cell carcinoma (RCC).

METHODS

A literature search was performed from inception until February 2016. Studies that reported relative risks, odd ratios, hazard ratios or standardized incidence ratio comparing the risk of RCC among HCV-infected participants *vs* those without HCV infection were included. Participants without HCV infection were used as comparators. Pooled odds ratios and 95%CI were calculated using a random-effect, generic inverse variance method.

RESULTS

Seven observational studies were with 196826 patients were included in the analysis to assess the risk of RCC in patients with HCV. A significantly increased risk of RCC among participants with HCV infection was found with a pooled RR of 1.86 (95%CI: 1.11-3.11). The association between RCC and HCV was marginally insignificant after a sensitivity analysis limited only to studies with adjusted analysis, with a pooled RR of 1.50 (95%CI: 0.93-2.42).

CONCLUSION

Our study demonstrated a potential association between HCV infection and RCC. Further studies of RCC

surveillance in patients with HCV are required.

Key words: Hepatitis C virus; Renal cancer; Kidney cancer; Systematic review; Meta-analysis

Core tip: Hepatitis C virus (HCV) is a leading cause of cirrhosis in the United States with a steadily increasing prevalence over the past two decades. Interestingly, HCV infection may also be associated with an increased risk of renal cell carcinoma (RCC) as observed in several epidemiologic studies. To further investigate this possible association, we conducted this systematic review and meta-analysis of observational studies reporting the risk of RCC among HCV-infected patients. We found a significantly increased risk of RCC among participants with HCV infection with the pooled risk ratio of 1.86 (95%CI: 1.11-3.11).

Wijarnpreecha K, Nissaisorakarn P, Sornprom S, Thongprayoon C, Thamcharoen N, Maneenil K, Podboy AJ, Cheungpasitporn W. Hepatitis C infection and renal cell carcinoma: A systematic review and meta-analysis. *World J Gastrointest Pathophysiol* 2016; 7(4): 314-319 Available from: URL: http://www.wjgnet.com/2150-5330/full/v7/i4/314.htm DOI: http://dx.doi.org/10.4291/wjgp.v7.i4.314

INTRODUCTION

Hepatitis C virus (HCV) remains the most common cause of chronic liver disease and cirrhosis worldwide and is one of the leading causes of chronic hepatitis and cirrhosis in the United States with a steadily increasing prevalence over the past two decades[1,2]. While commonly associated with hepatocellular carcinoma[2], hepatitis C infection is associated with extrahepatic malignancies including cholangiocarcinoma, non-Hodgkin's lymphoma and possibly myeloma[3-5]. The oncogenic properties of hepatitis C are hypothesized to be secondary to chronic antigenic stimulation of the immune system, promotion of a chronic inflammatory state or direct oxidative stress[6]. Besides, chronic HCV infection has also been linked to a myriad of extrahepatic diseases including increasing the risk of renal disease and increasing the prevalence of chronic kidney disease up to 40% higher compared to non-infected patients[7,8].

Renal cell carcinoma (RCC), arising from the renal cortex is responsible for 80% of all renal malignancies and accounts for approximately 14000 deaths each year in the United States[9]. The risk factors for RCC such as acquired cystic kidney disease, smoking, kidney stones, obesity, hereditary factors have been described[10-14]. The epidemiological studies have demonstrated an increasing incidence of RCC, particularly in African Americans[15].

Secondary to the oncogenic nature of Hepatitis C, several studies have linked chronic infection with an increased risk for development of RCC[16-22]. However, the findings from these studies were contradictory. Thus, we performed this meta-analysis to examine the risk of RCC in HCV-infected patients.

MATERIALS AND METHODS

Literature search

Two investigators (Karn Wijarnpreecha and Wisit Cheungpasitporn) independently reviewed published studies indexed in MEDLINE, EMBASE, and the Cochrane database from their inception to February 2016 using the search strategy that included the terms for "hepatitis" and "renal cancer" as described in Item S1 in online supplementary data. No limitation on language was applied. A manual search for additional studies using references of selected retrieved articles was also performed. Three investigators (Karn Wijarnpreecha, Charat Thongprayoon and Wisit Cheungpasitporn) independently reviewed the titles and abstracts of the studies identified in the search based on inclusion and exclusion criteria. The full text of the included studies from the first phase was reviewed independently to ascertain whether or not they matched the inclusion criteria. We also performed a manual search of conference proceedings from major gastroenterology and hepatology meetings for additional abstracts on the topic. When additional information was needed, we contacted the corresponding investigators of eligible studies.

Study selection

The inclusion criteria were as follows: (1) observational studies assessing the association between hepatitis C and RCC; (2) odds ratios, relative risks or hazard ratios with 95%CI were provided; and (3) individuals without HCV infection were used as comparators in cohort studies while individuals without RCC were applied as comparators in the cross-sectional and case-control studies.

Study acceptability was individually defined by the three investigators mentioned above. Disagreements in the ascertainment of study eligibility were settled by joint agreement. Also, the quality of each study was individually appraised by each investigator. We used the validated Newcastle-Ottawa quality assessment scale for cohort and case-control studies[23] and modified Newcastle-Ottawa scale[24] for the cross-sectional study.

Data extraction

A data collection report was utilized to derive the information from each study including name of title and the first author, year of study and publication, country, demographic data of the participants, number of participants, method used to diagnose the HCV infection and RCC, effect estimates (odds ratios, relative risks or hazard ratios) with 95%CI, and factors adjusted in the multivariate analysis. To assure the certainty, this data

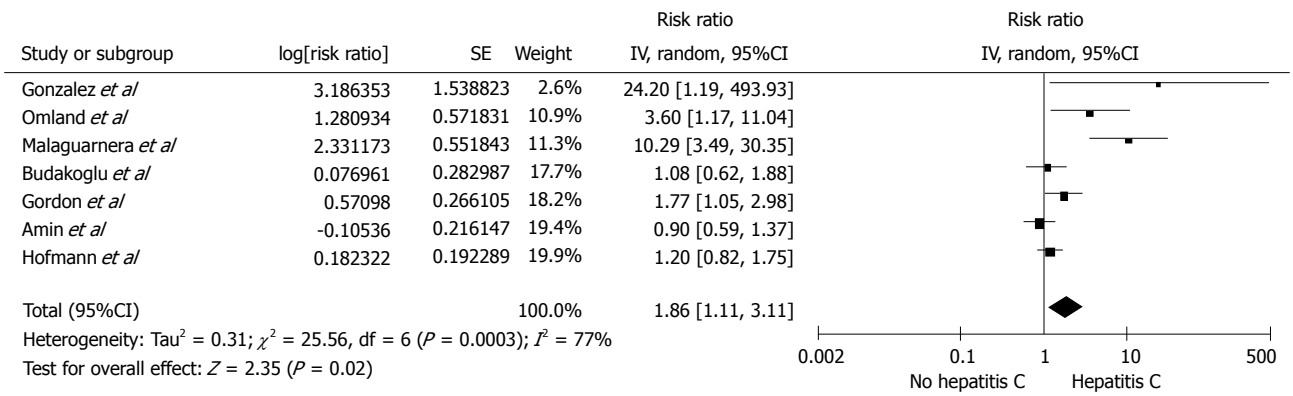

Figure 1 Forest plot of all included studies of the association between hepatitis C infection and renal cell carcinoma. Square data markers represent risk ratios (RRs); horizontal lines, the 95%CI with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall RR and 95%CI for the outcome of interest.

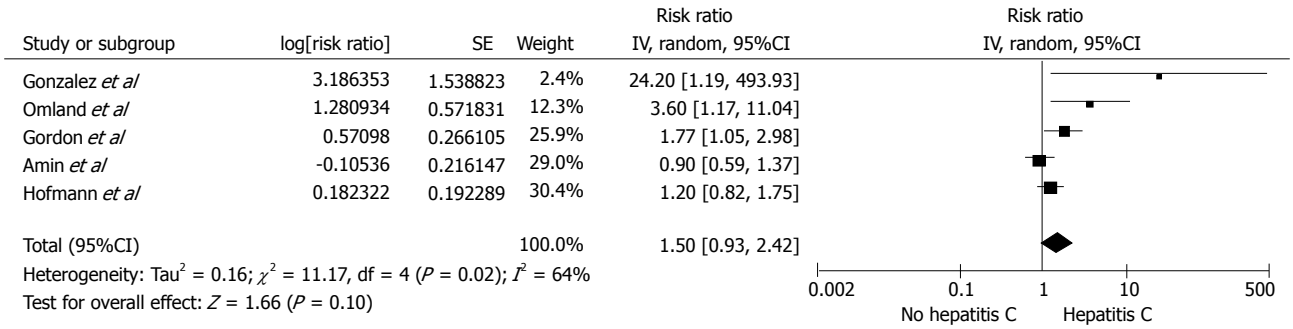

Figure 2 Forrest plot of all included studies in sensitivity analysis of the association between hepatitis C infection and renal cell carcinoma. Square data markers represent risk ratios (RRs); horizontal lines, the 95%CIs with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall RR and 95%CI for the outcome of interest.

extraction process was reviewed by all investigators.

Statistical analysis

Review Manager (RevMan) 5.3 software from the Cochrane Collaboration was utilized for meta-analysis. Generic inverse variance (DerSimonian and Laird) method[25] was employed to combined adjusted point estimates and standard errors from each study. We used a random-effect model due to the high likelihood of between-study variance from different study designs and populations. Cochran's *Q* test and I^2 statistic were used to determine the between-study heterogeneity. A value of I^2 of 0%-25%, 25%-50%, 50%-75%, and greater than 75% embodied insignificant, low, moderate and high heterogeneity, respectively[26].

RESULTS

Of 5778 potentially relevant articles, 5582 articles were excluded by the title and abstract not fulfilling inclusion criteria due to the type of article, study design, population, or outcome of interest. Additionally, 189 articles were excluded (35 articles were not observational studies, and 154 articles did not describe the outcomes of interest, Macleod *et al*[27]'s study did not contain data on specific viral hepatitis{Macleod, 2013 #83}). Finally, seven observational studies (4 cohort and 3 case-controlled studies) with 196826 patients were included in the meta-analysis[16-22]. Item S2 describes the study selection flow. The characteristics and quality appraisal of the included studies of HCV and RCC are shown in Table 1. Four studies were conducted in Europe, 2 in the United States, and 1 in Australia.

The risk of renal cell carcinoma in patients with hepatitis C virus infection

Among individuals with HCV infection, there was a significantly increased risk of RCC with the pooled risk ratio (RR) of 1.86 (95%CI: 1.11-3.11, I^2 =77%), as demonstrated in Figure 1. The statistical heterogeneity was high with an I^2 of 77%. The association between RCC and HCV was marginally insignificant after the sensitivity analysis including only studies with confounder adjustment[16,18-20,22] with a pooled RR of 1.50 (95%CI: 0.93-2.42, I^2 =64%), as shown in Figure 2.

Evaluation for publication bias

Two authors (Karn Wijarnpreecha and Wisit Cheungpasitporn) independently performed the assessment of the risk of bias of the included studies. Only minor disagreements between 2 reviewers were present and were resolved by discussion and consensus. A funnel plot was constructed to assess publication bias for the risk of RCC in HCV-infected patients (Figure S1). The

Table 1 Main characteristics of the studies included in this meta-analysis

Ref.	Country	Study design	Year	Total number	Study sample	Exposure definition	Exposure measurement	Outcome definition	Outcome ascertainment	Adjusted OR	Confounder adjustment	Quality assessment (Newcastle-Ottawa scale)
Amin *et al*[16]	Australia	Cohort study	2006	75834 in HCV patients	People notified with HCV infection to the New South Wales Health Department's Notifiable Diseases Database between 1 January 1990 and 31 December 2002 (HCV group) and NSW population (control group)	HCV infection	Detection of anti-HCV antibody or HCV RNA	Renal cancer or kidney cancer	The NSW Central Cancer Registry with ICD-10 code C64 for kidney cancer and C65 for renal cancer	Kidney cancer 0.9 (0.6–1.4)	Age, sex and calendar year	Selection: 4 Comparability: 1 Outcome: 3
Malagu arnera *et al*[21]	Italy	Case control study	2006	315 (15 case and 300 control)	Elderly kidney cancer patients attending geriatric department (case) and elderly volunteers (control)	Positive Anti-HCV	Detection of Anti-HCV antibody using enzyme-linked immunosorbent assay. Assay positive samples were confirmed by immunoblotting	Kidney cancer	N/A	10.29 (3.49-30.36)	None	Selection: 3 Comparability: 0 Outcome: 2
Omland *et al*[22]	Denmark	Cohort study	2010	4204 in HCV patients	Acute or chronic HCV infected patients listed in the Danish National Hospital Registry between 1994 and 2003 without previous diagnosis of cancer (HCV) and general population (control)	Acute or chronic HCV infection	ICD-10 code (B17.1 and B18.2) from the Danish National Hospital Registry	Kidney cancer	The Danish Cancer Registry with ICD-7 code 180	3.60 (0.98–9.22)	Age, sex and year of diagnosis	Selection: 4 Comparability: 1 Outcome: 2
Gordon *et al*[19]	United States	Cohort study	2010	67063	HCV-tested patients (both positive and negative) between 1997 and 2006 from administrative data from Henry Ford hospital	HCV infection	Positive anti-HCV test using enzyme-linked immunosorbent assay, confirmed by a documented positive molecular assay for HCV RNA	Renal cell carcinoma	Health system cancer registry, confirmed by medical record and pathology report review	1.77 (1.05-2.98)	Age, race, gender, chronic kidney disease	Selection: 4 Comparability: 1 Outcome: 3
Budakoğlu *et al*[17]	Turkey	Case-control study	2011	6170 (903 case and 5267 control)	Patients who had histologically proven renal cell carcinoma diagnosis between 2005 to 2010 from six tertiary cancer centers (case) and healthy people who were living in the same geographic regions (control)	Positive anti-HCV	Positive anti-HCV test using enzyme-linked immunosorbent assay	Renal cell carcinoma	Histopathology report	1.08 (0.62-1.88)	None	Selection: 3 Comparability: 0 Outcome: 3
Hofmann *et al*[20]	Sweden	Cohort study	2011	43000 in HCV patients	All Swedish residents diagnosed with HCV infection between 1990 and 2006 (HCV group) and general population (control)	Chronic HCV infection	The national surveillance database at the Swedish Institute for Infectious Disease Control	Kidney cancer	The national Cancer register with ICD-7 code 180.0 and 180.9 and histologic confirmation	1.2 (0.8–1.7)	Age, sex and calendar year	Selection: 4 Comparability: 1 Outcome: 3
Gonzalez *et al*[18]	United States	Case-control study	2015	240 (140 case and 100 control)	Newly diagnosed renal cell carcinoma (case) and newly diagnosed colon cancer patients (control)	Chronic HCV infection	Detection of anti-HCV antibody or HCV RNA	Renal cell carcinoma	Histopathology report	Positive HCV RNA 24.20 (2.4 - > 999.9)	Sex, age, race, BMI, smoking, alcohol abuse, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, congestive heart failure, chronic kidney disease, cirrhosis	Selection: 3 Comparability: 2 Outcome: 3

BMI: Body mass index; DNHR: Danish National Hospital Registry; ELISA: Enzyme-linked immunosorbent assay; HCV: Hepatitis C virus; N/A: Not available; NSW: New South Wales; RCC: Renal cell carcinoma; SIR: Standardized incidence ratio.

funnel plot was suggestive of a small publication bias toward studies with a positive correlation between HCV infection and RCC.

DISCUSSION

This meta-analysis was conducted to summarize all presently available data on the association between HCV infection and RCC. Our study demonstrated a 1.86-fold increased risk of RCC among participants who had HCV infection compared to those without HCV infection. Our analysis also illustrates that that RCC patients with HCV were significantly younger than RCC patients without HCV. The results of our study reinforce the hypothesis that HCV may accelerate the risk of developing RCC.

Although the nature in which HCV induces RCC is not entirely understood, several hypotheses exist. A recent bioinformatics study demonstrated a plausible biological relationship between HCV infection and the development of RCC *via* the NY-REN-54 protein. The NY-REN-54 protein which is an altered ubiquitin-related protein that plays a role in the disturbance impairs the autophagic response *via* to the ubiquitin-protein ligase-related self-regulatory mechanism, which in turn promotes oncogenesis[28]. Additionally, inhibition of cytotoxic T-lymphocyte-dependent apoptosis by the hepatitis virus secondarily leads to a disturbance in host immunity and normal tissue homeostasis leading to carcinoma formation[29]. Lukkonen *et al*[30] demonstrated an increased expression of serine protease inhibitor Kazal (SPIK), a cellular protein that inhibits serine protease-related apoptosis, in RCC tissue samples as an additional mechanism for HCV-induced RCC.

There are several limitations in our study. Firstly, there was a high amount of statistical heterogeneity present in the completed analysis. The potential source of this heterogeneity includes variation in confounder-adjusted methods (*e.g.,* age, sex, ethnicity, and chronic kidney disease), exposure measurement, outcome ascertainments, and follow-up duration. Secondly, it should be noted that there was a potential small publication bias with a positive association between HCV infection and RCC. The possibility of selection bias could play a role in chart-reviewed population base study. Finally, this meta-analysis of observational studies could only show an association. It cannot establish causality as an unknown number of confounders could play a role in the association between HCV and RCC.

In summary, this study demonstrates a potential association between HCV infection and RCC. In the new era of treatment of HCV infection, direct-acting antiviral agents have been demonstrated to be effective therapy and increasingly used[31]. These agents may potentially decrease the incidence of RCC in HCV patients in the long term.

COMMENTS

Background

Hepatitis C virus (HCV) is one of the leading causes of cirrhosis as the prevalence of HCV has been steadily increasing over the past two decades in the United States. Extrahepatic manifestations of HCV are common. Interestingly, HCV infection could also increase the risk of renal cell carcinoma (RCC) as observed in several epidemiologic studies.

Research frontiers

The results of those epidemiologic studies were inconsistent. To further investigate this possible association of HCV and RCC, the authors conducted this systematic review and meta-analysis of observational studies reporting the risk of RCC among HCV-infected patients.

Innovations and breakthroughs

The authors found a significantly increased risk of RCC among participants with HCV infection with the pooled risk ratio (RR) of 1.86 (95%CI: 1.11-3.11). The sensitivity analysis including only studies with confounder adjustment also demonstrated increased risk of RCC among participants with HCV infection with the pooled RR of 1.50 (95%CI: 0.93-2.42) even though without reaching statistical significance.

Applications

This study demonstrated a potential association between HCV infection and RCC. This finding suggests that a history of HCV is potentially associated with RCC and may impact clinical management and cancer surveillance.

Peer-review

The manuscript is an interesting meta-analysis about the correlation of HCV infection and RCC development. The aim of the meta-analysis is clearly stated and methods are well-described.

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