

Association between the presence of *H pylori* in the liver and hepatocellular carcinoma: A meta-analysis

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Received: June 28, 2007

Revised: October 13, 2007

analysis; Publication bias

<http://dx.doi.org/10.3748/wjg.14.307>

Xuan SY, Xin YN, Chen AJ, Dong QJ, Qiang X, Li N, Zheng MH, Guan HS. Association between the presence of *H pylori* in the liver and hepatocellular carcinoma: A meta-analysis. *World J Gastroenterol* 2008; 14(2): 307-312

<http://www.wjgnet.com/1007-9327/14/307.asp>

Abstract

AIM: To evaluate the arguments for and against the possible roles of *H pylori* in hepatocellular carcinoma (HCC).

METHODS: We performed a systematic review of all relevant studies published in the literature. A total of 103 clinical trials and reports were identified, but only 10 trials qualified under our selection criteria. A meta-analysis was carried out by a biostatistician according to the Cochrane Reviewers' Handbook recommended by The Cochrane Collaboration.

RESULTS: Nine case-control studies and one retrospective cross sectional study were included in the final analysis. Overall the prevalence of *H pylori* infection was 53.3% (129 of 242) in cases and 10.4% (29 of 280) in controls, and the summary odds ratio for the association of *H pylori* infection with the risk for HCC (using the fixed-effects model, which accounted for the homogeneity across the 10 studies) was determined to be 13.63 (95% CI, 7.90-23.49).

CONCLUSION: Our analysis showed a positive association between *H pylori* infection and the risk of HCC, with an indication of possible publication bias and possible confounders due to study designs that showed results of less pronounced associations.

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Key words: *H pylori*; Hepatocellular carcinoma; Meta-

INTRODUCTION

The profound impact of hepatocellular carcinoma (HCC) on human health is known worldwide^[1]. Persistent hepatitis B virus (HBV) and hepatitis C virus (HCV) infections and aflatoxins are the main causes of HCC^[2]. The real risk factors for HCC may be far more numerous than the known causes. The infectious agent *Helicobacter hepaticus* (*H hepaticus*), for example, first described by Ward *et al* in 1994, has recently received new attention for its role in causing chronic active hepatitis and associated liver tumors^[3].

Since *H pylori* was first cultivated from a human gastric biopsy specimen in 1982, it has become apparent that *H pylori* infection is correlated with gastric cancer and mucosa-associated lymphoid tissue lymphoma. More recently, researchers have reported that *Helicobacter spp.* have been identified in liver tissue resected from patients with HCC^[4]. Experimental infection by *Helicobacter hepaticus* in mice causes chronic hepatitis and HCC. It is highly noteworthy that *H pylori* was found in liver tissues resected from patients with HCC^[5-7].

The question of whether *H pylori* could play a role in the development of HCC remains controversial. Many conflicting reports have been published to date; thus, we performed a systematic review of all of the relevant studies published in the literature to evaluate the arguments for and against the possible roles of *H pylori* in HCC.

MATERIALS AND METHODS

Selection criteria

We searched different databases, including the *Cochrane Controlled Trials Register on The Cochrane Library* Issue 1, 2007, MEDLINE (January, 1989-March, 2007), EMBASE.com (January, 1989-March, 2007) and the China Biological Medicine Database (CBMdisc) (January, 1989-March,

Table 1 Characteristics of 10 studies investigating the association between the presence of *H pylori* infection in liver and hepatocellular carcinoma

Reference	Country, year of publication	<i>H pylori</i> positivity/total subjects		Type of controls (<i>n</i>)	Age range (mean), yr	
		Cases	Controls		Cases	Controls
Pellicano <i>et al</i> ^[6]	Italy, 2004	17/20	2/6	Metastatic cancer (<i>n</i> = 6)	NA	NA
Ito <i>et al</i> ^[7]	Japan, 2004	13/15	0/17	Cirrhotic liver tissue specimens (<i>n</i> = 10), normal liver tissue specimens (<i>n</i> = 7)	36-73 (59.2)	NA
Coppola <i>et al</i> ^[8]	Italy, 2003	0/21	0/34	Metastatic liver carcinoma (<i>n</i> = 7), chronic hepatitis (<i>n</i> = 27)	NA	NA
Dore <i>et al</i> ^[9]	Italy, 2002	6/11	5/30	Chronic viral hepatitis without (<i>n</i> = 18) or with (<i>n</i> = 12) cirrhosis	19-78 (54.9)	49-78 (65.2)
Avenaoud <i>et al</i> ^[10]	France, 2000	8/8	1/8	Patients without primary liver carcinoma (<i>n</i> = 8)	NA	NA
Nilsson <i>et al</i> ^[11]	Sweden, 2001	12/16	0/20	Metastatic liver carcinoma (<i>n</i> = 20)	NA	NA
Zhang <i>et al</i> ^[12]	China, 2004	16/48	2/37	Liver cirrhosis (<i>n</i> = 12), pericarcinomatous tissues (<i>n</i> = 10), benign tumor of liver (<i>n</i> = 9), chronic hepatitis (<i>n</i> = 6)	25-67 (46.5)	35-65 (42.5)
Huang <i>et al</i> ^[13]	China, 2004	16/38	0/30	Liver cirrhosis (<i>n</i> = 15), benign tumor of liver (<i>n</i> = 15)	NA	NA
Li N <i>et al</i> ^[14]	China, 2006	22/34	0/20	Liver external injury (<i>n</i> = 5) giant hemangioma (<i>n</i> = 5), macrosis hepatic cyst (<i>n</i> = 3), intrahepatic bile duct stone (<i>n</i> = 7)	28-71 (52)	30-68 (48)
Rocha <i>et al</i> ^[15]	France, 2005	19/31	19/78	Non-cirrhotic chronic hepatitis C (<i>n</i> = 24), HCV Positive cirrhosis without HCC (<i>n</i> = 29), HCV Positive cirrhosis and HCC (<i>n</i> = 25)	NA	NA

2007), for the terms ‘hepatocellular carcinoma’ and ‘*H pylori*’. The reference lists of pertinent reviews and retrieved articles were also checked for the identification of additional studies. We also performed a full manual search from the bibliographies of selected papers. Studies were identified by two researchers, independently; the two lists were compared and discrepancies were resolved. We also contacted the authors of studies containing relevant information, who did not report the results necessary for this analysis. Unpublished data were also accepted if an abstract was available and further information was obtained from the author.

In the meta-analysis, the following inclusive selection criteria were set and reviewed by two independent investigators: (1) each trial is an independent case-controlled study; (2) the purpose of all studies and statistical methods is similar; (3) the numbers of cases, controls and positive rate of *helicobacter* (the presence of *H pylori* DNA sequences in human liver or other standard methods for definition of *H pylori* infection in the liver) are concrete; (4) the study groups have definite HCC by pathology, histology and operation; (5) only studies that selected HCC patients as cases and subjects with other liver diseases or normal liver tissue specimens as controls are included.

The following exclusive selection criteria were set: (1) incomplete raw data; (2) repetitive reports (if more than one version of the same study was retrieved, only the most recent is used); (3) the positive rate of *helicobacter* is not detected by the presence of *H pylori* DNA sequences or other standard methods for detection of *H pylori* infection in liver (that is, all subjects are tested for the presence in serum of IgG antibodies against *H pylori*).

A total of 103 clinical trials and reports were identified and only 10 trials^[6-15] qualified on the basis of our selection criteria. The studies were independently evaluated by two researchers. Discrepancies in the evaluations of some studies were resolved by discussion between the reviewers.

The main features of the trials included in the meta-analysis are shown in Table 1.

Data extraction and outcomes

Data extracted included year of publication, country of origin, number of cases and controls, characteristics of controls, age of participants, prevalence of *H pylori* infection in cases and controls, and reported odds ratios (OR). All available studies were reviewed by two investigators independently. Reference 18 is a retrospective cross-sectional study; the others are case-controlled studies.

Statistical analysis

The meta-analysis was carried out by a biostatistician (Chen AJ) according to the Cochrane Reviewers’ Handbook recommended by The Cochrane Collaboration. First, a pooled OR was calculated using the fixed-effect model. The heterogeneity of the studies was examined using the DL Q statistic^[16]. Because the results were homogeneous ($P = 0.07$), a fixed-effects model was employed using the DerSimonian and Laird (DL) methods. A pooled OR was presented as a standard plot with 95 percent confidence intervals (CI). Begg and Mazumdar’s proposed adjusted rank correlation test^[17] and Egger’s linear regression approach^[10] were used to measure publication bias, which was shown as a funnel plot (Figure 1). Fixed (Figure 2A) and random-effects models (Figure 2B) were also used to perform sensitivity-analysis to assess the reliability of meta-analysis. The statistical package RevMan version 5.0 (provided by The Cochrane Collaboration, Oxford, England) was used for statistical analyses.

RESULTS

Nine case-controlled studies and one retrospective cross-sectional study were identified and reviewed, as shown in Table 1^[6-15].

In the meta-analysis, the overall prevalence of *H pylori* infection was 53.3% (129 of 242) in cases and 10.4% (29 of 280) in controls, and a summary OR for the association of *H pylori* infection with the risk for hepatocellular carcinoma (using the fixed-effects model, which accounted for the homogeneity across the 10 studies) was determined to be 13.63 (95% CI, 7.90-23.49) (Figure 2A). Figure 2A shows the ORs and 95% CIs of each study, and the summary OR determined by meta-analysis. The proportion of the total variation in study estimates, because of heterogeneity, was 44.0% (heterogeneity test statistics $\chi^2 = 14.28$, on 8 df, $P = 0.07$, $I^2 = 44.0\%$). A random-effects model was also used to perform sensitivity-analysis to assess the reliability of meta-analysis, as shown in Figure 2B.

Graphical and statistical evaluation of publication bias

Publication bias was assessed for all pooled ORs with confidence intervals using Begg's test^[17,18]. This bias is shown as a funnel plot in Figure 1.

The funnel plot method was used to assess the possible presence of publication bias^[19,20]. It consists of plotting each study's OR on a logarithmic scale (horizontal axis) against its SE (vertical axis), with an informal visual examination of the funnel plot graph to check for funnel plot asymmetry as an indication of potential publication bias. Studies of smaller size normally have a wider distribution of results than larger studies, because of a higher degree of random variation, and the ORs scatter more widely at the bottom of such a graph, with the spread narrowing with increasing precision among larger studies. In the absence of a publication bias, the graph appears as a symmetrical inverted funnel, as the risk estimates should be symmetrically distributed around the midpoint value (that is, the summary OR). Publication bias may occur if smaller studies showing no significant results remain unpublished, leading to an asymmetrical appearance of the funnel plot with a gap at the bottom of the graph.

DISCUSSION

H pylori infection is a classical model with which to study cancer development as a consequence of chronic inflammation. The estimated total of infection-attributed malignancies per year is 1.9 million cases or 17.8% of the global cancer burden^[21]. Among the principal carcinogenic agents, *H pylori* is a leading factor, being responsible for 5.5% of all cancers. *H pylori* was classified as a type I carcinogen by the International Agency for Research on Cancer in 1994^[22]. A striking finding indicated by Ward *et al* is that bacterial infection of the liver in healthy A/JCr male mice is capable of inducing a strong inflammatory change in the parenchyma (for example, hepatitis) leading to HCC.

We analyzed the published evidence investigating the association between *H pylori* infection and HCC. Studies concerning this possible association have been undertaken since the early 2000s. To our knowledge, this is the first published meta-analysis investigating this association. The summary OR for the association of evidence of *H pylori*

Review: the association between *H pylori* and hepatocellular carcinoma
Comparison: 01 hepatocellular carcinoma group versus control group
Outcome: 01 status of *H pylori* infection

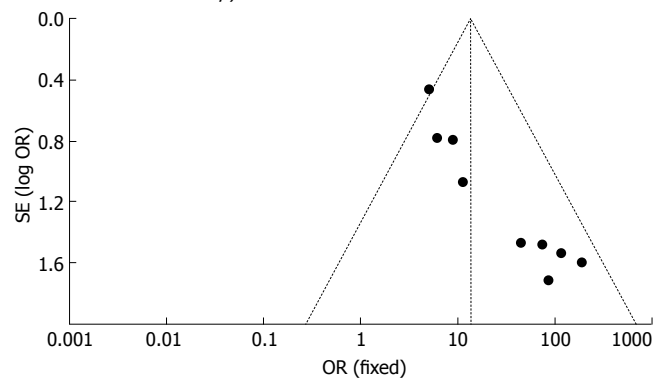


Figure 1 Funnel plot to explore publication bias. The graphical funnel plot of the 10 published studies appears to be asymmetrical.

infection and the risk for HCC was estimated to be 13.63 with a 95% CI from 7.90 to 23.49, with a confound of study design (lower for studies of prospective design and higher for retrospective case-controlled studies).

In our study, only publications in English or Chinese were used for evaluation. 'Meta-analytical' research on 29 meta-analyses investigating language bias has provided evidence that the OR estimated in meta-analyses from non-English publications are on average 0.8-fold (95% CI, 0.7-1.0) the OR estimates from English-written publications^[23]. Therefore, even if we had not searched for non-English publications, this might have introduced only a small bias in the overall findings, which, in our opinion, would not have altered our main conclusions.

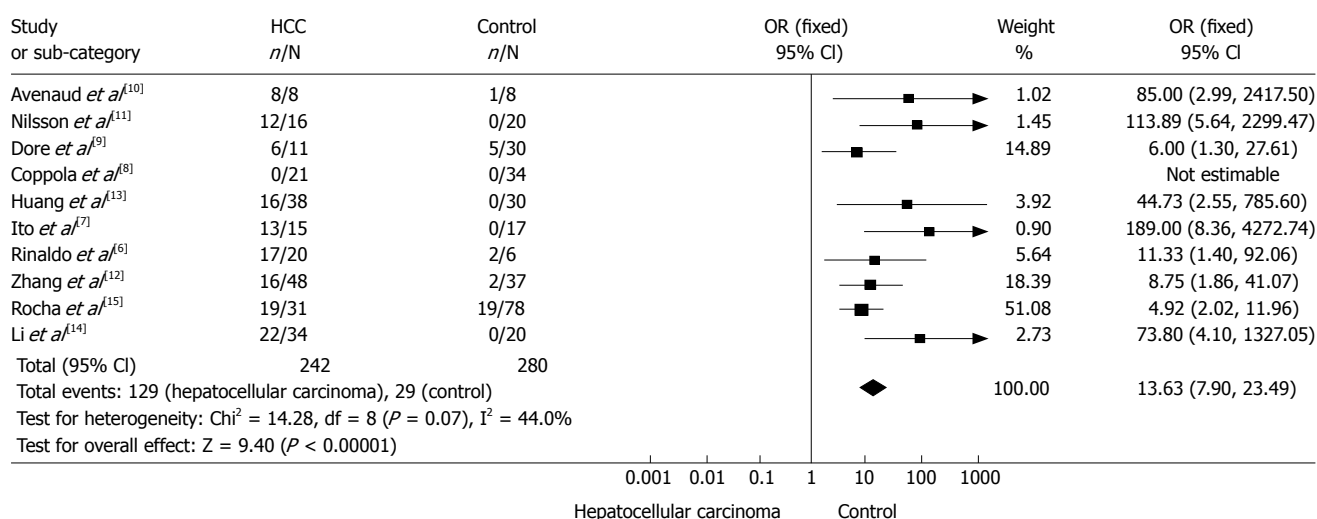
Several other points should be considered when interpreting the results of our study.

First, the positive rate of *helicobacter* of the most studies was detected by the presence of *H pylori* DNA sequences. Polymerase chain reaction (PCR) amplification using two sets of primers located in the 16S ribosomal DNA (rDNA) was used to detect the presence of bacteria, but this is not a 'gold standard' method for detecting *H pylori* infection in the liver. Histology with standard stains and culturing maybe more precise than 16S rDNA; however, false negatives are likely. Research in this area has been limited by the lack of a gold standard for the diagnosis of these organisms in the liver. Most published data to date have been based on molecular techniques that detect the DNA of *Helicobacter* species in liver tissues, rather than evidence of viable organisms in the liver.

Secondly, Reference 18 is a retrospective cross-sectional study, whereas the other studies are case-controlled studies. Such studies are generally lower in quality for use as prospective design studies and higher in quality as retrospective case-controlled studies. These observational studies are more prone to bias than randomized clinical trial (RCT) studies.

Third, in this analysis, graphical and statistical methods for testing and adjusting for a possible publication bias and a test for potential heterogeneity between studies were performed. A graphical funnel plot of the 10 published studies was asymmetrical, which may suggest the probable

A Review: the Association between *H pylori* and hepatocellular carcinoma
Comparison: 01 hepatocellular carcinoma group versus control group
Outcome: 01 status of *H pylori* infection



B Review: the Association between *H pylori* and hepatocellular carcinoma
Comparison: 01 hepatocellular carcinoma group versus control group
Outcome: 01 status of *H pylori* infection

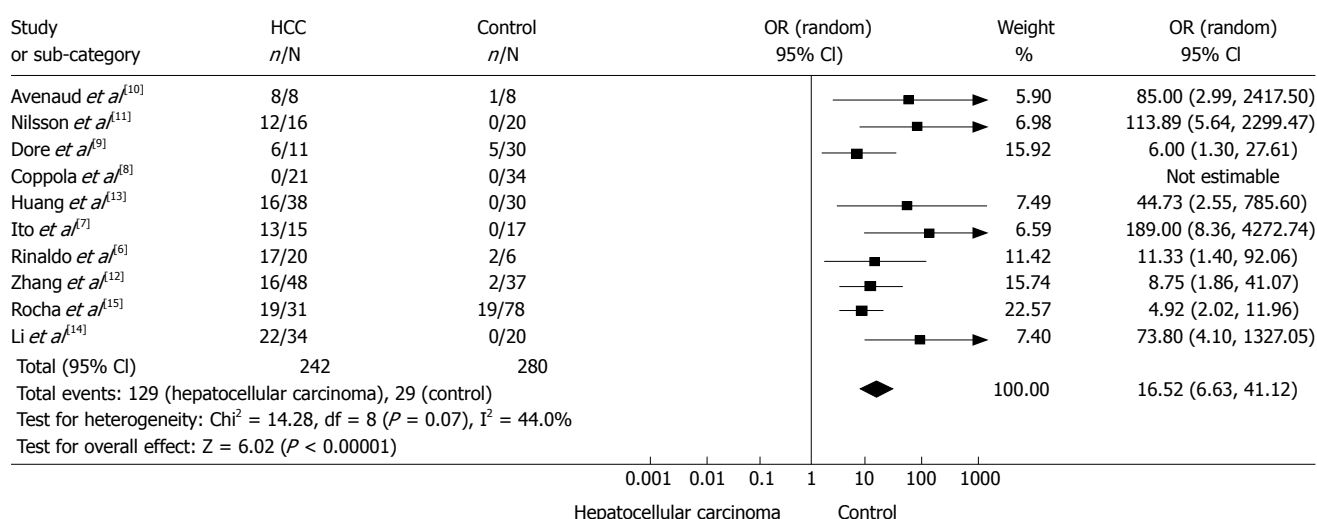


Figure 2 A: Forest plot of a meta-analysis of the association between *H pylori* and hepatocellular carcinoma risk (fixed-effects mode). It shows the ORs and 95% CI of each study, and the summary OR determined by meta-analysis. The proportion of total variation in study estimates, because of heterogeneity, was 44.0% (heterogeneity test statistics $\chi^2 = 14.28$, on 8 df, $P = 0.07$, $I^2 = 44.0\%$); **B:** Sensitivity-analysis: A Forest plot of a meta-analysis of the association between *H pylori* and hepatocellular carcinoma risk (random-effects mode).

existence of publication bias, although this may occur if some studies showing no significant results remained unpublished or if such negative studies are few.

Additionally, because the information used in our research was based on data from observational studies, the characteristics of each study population and the different methodologies of these studies should be taken into account when interpreting the results of our analysis. For example, different inclusion criteria for selection of the participants might have influenced the results of this research. Differences in the age distribution, different countries and different types of control groups (cirrhotic patients, patients with chronic viral hepatitis without or with cirrhosis, patients without primary liver carcinoma, patients with metastatic liver carcinoma, pericarcinomatous tissues, benign tumors of the liver, liver external

injuries, giant hemangiomas, macrosis hepatic cysts, and intrahepatic bile duct stones) could also be among the potential causes of variation in the studies' estimates.

Most studies did not control for the matching variables in the analysis, and the risk for HCC was not controlled for possible confounders such as HBV or HCV, except in Reference 18.

Only the articles of Dore *et al*^[9] and Rocha *et al*^[15] demonstrated the association of *Helicobacter* species with hepatitis C cirrhosis and HCC. These two studies included a large series of patients and examined both tumor and cirrhotic liver tissue samples from patients with HCV-positive HCC. *Helicobacter* DNA was found in a small percentage of liver biopsies from controls as well as from patients with chronic hepatitis C (4.2% and 3.5%, respectively). However, the prevalence of *Helicobacter*

species was high in patients with HCV-positive cirrhosis and in those with cirrhosis and HCC (68% and 61%, respectively). In nearly all cancer tissues, *Helicobacter* DNA was detected and identified as *Helicobacter pullorum* or *H pylori*-like organisms. The authors suggested a possible causal role of these bacteria in the progression of chronic hepatitis C and the development of HCC.

Furthermore, although we tried to maximize our efforts to identify all relevant published studies in peer-reviewed journals, it is possible that some escaped our attention.

There is some evidence to suggest that *Helicobacter* infection may be associated with an increased risk of extra-gastric malignancies^[24]. The presence of *Helicobacter* species in liver tissues from patients with different liver diseases, including hepatic neoplasias, has been reported by numerous authors. The most intriguing hypothesis is that these bacteria might play a role in the development of HCC^[25].

Despite its limitations, the present analysis has some implications: as relatively few studies are available in this field and current evidence remains limited, the necessity to conduct large studies with an adequate methodological quality, properly controlling for possible confounds in order to obtain valid results, should be emphasized; for example, tissue from unaffected liver metastatic carcinoma could be used as a suitable control.

In conclusion, our analysis showed a positive association between *H pylori* infection and the risk of HCC. We obtained from our meta-analysis a summary OR of 13.63 for the association of *H pylori* infection and HCC, with an indication of possible publication bias and confounds of study design, with less pronounced associations in prospective studies than in retrospective studies. Therefore, this risk increase should be interpreted with caution. Better designed and better controlled studies are needed to clarify the strength of this association and the possible causal role of *H pylori* infection in patients with HCC, and further prospective studies are required to prove this hypothesis. Given the importance of this potential association, further verification is warranted.

COMMENTS

Background

The real risk factors for hepatocellular carcinoma (HCC) may be far more than the known causes. A new infectious agent, *Helicobacter hepaticus* (*H hepaticus*), causing chronic active hepatitis and associated liver tumors, has been described by Ward *et al.* The question of whether *H pylori* could play a role in the development of HCC remains controversial. Many conflicting reports have been published to date, so we performed a systematic review of all of the relevant studies published in the literature to evaluate the arguments for and against the possible roles of *H pylori* in HCC.

Research frontiers

Since *H pylori* was first cultivated from human gastric biopsy specimens in 1982, it has become apparent that *H pylori* infection is correlated with gastric cancer and mucosa-associated lymphoid tissue lymphoma. More recently, researchers have reported that *Helicobacter* spp. were identified in liver tissue resected from patients with HCC. Experimental infection by *Helicobacter hepaticus* in mice causes chronic hepatitis and HCC. It is highly noteworthy that *H pylori* was found in liver tissue resected from patients with HCC.

Innovations and breakthroughs

To our knowledge, this is the first published meta-analysis investigating the

association between *H pylori* and hepatocellular carcinoma risk.

Applications

Our analysis showed a positive association between *H pylori* infection and the risk of hepatocellular carcinoma, with an indication of possible publication bias and confound of study design, with less pronounced associations in prospective studies than in retrospective studies. Therefore, this risk increase should be interpreted with caution; better designed and better controlled studies are needed to clarify the strength of the association and the possible causal role of *H pylori* infection in hepatocellular carcinoma. Further prospective studies are requested to prove this hypothesis; given the importance of this potential association, further verification is warranted.

Terminology

Meta analysis: In statistics, a meta-analysis combines the result of several studies that address a set of related research hypotheses. *H pylori*: *H pylori* is a bacteria that can cause digestive illnesses, including gastritis and peptic ulcer disease. More recently, researchers have reported that *Helicobacter* spp. were identified in liver tissue resected from patients with hepatocellular carcinoma.

Peer review

Authors evaluated the arguments for and against the possible roles of *H pylori* in HCC through a systematic review of all relevant studies published in the literature. The analysis showed a positive association between *H pylori* infection and the risk of HCC.

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S- Editor Zhu LH L- Editor McGowan D E- Editor Lu W