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Hepatitis C virus genotype 1b as a risk factor for hepatocellular carcinoma development: A meta-analysis☆

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***Background/Aims*: Hepatitis C virus (HCV) is a known risk factor for hepatocellular carcinoma (HCC), but whether the risk varies among patients infected with different HCV genotypes is still controversial. We performed a meta-analysis to clarify whether the genotype 1b is associated with a higher risk of HCC than other genotypes.**

***Methods*: We identified 57 relevant papers through a literature search to December 2007 but, since age could represent a major confounder, we focused the meta-analysis on the 21 studies presenting age-adjusted risk estimates for HCV genotype 1b vs. other genotypes. We used random-effects models with the DerSimonian–Laird method and assessed heterogeneity between studies and publication bias.**

***Results*: Patients infected with HCV genotype 1b have almost double the risk to develop HCC than those infected with other genotypes (Relative Risk (95% Confidence Intervals) = 1.78(1.36–2.32)). The pooled risk estimate was somewhat lower when we restricted the analysis to the eight studies conducted in patients with liver cirrhosis (1.60;1.07–2.39) or considering the 36 studies presenting only crude data (1.63;1.30–2.06). In seven studies excluding patients with liver cirrhosis, the RR (95% CI) increased to 2.46(1.69–3.59).**

***Conclusions*: This meta-analysis suggests that HCV genotype 1b plays an important role in HCC development, especially in patients with early stage liver disease.**

***Keywords*: Epidemiology; Liver cancer; Virology**

1. Introduction

Approximately 20% of patients with HCV infection will develop cirrhosis after a mean period of 20 years, and 1–4% of them will eventually develop hepatocellular carcinoma (HCC) on average 30 years after infection [1,2]. HCC represents the most serious complication of Chronic Liver Disease (CLD) and the most frequent cause of death in patients with compensated liver cirrhosis (LC) [3]. Besides HCV infection, other well known risk factors for HCC include infection with hepatitis B virus (HBV), high ethanol intake, older age, male gender, tobacco smoking, LC, advanced fibrosis stage, high histological activity score and elevated alanine aminotransferase serum levels [4–9].

In this setting, the impact of HCV genotypes has also been evaluated in several studies. Despite some of them reported that patients infected with HCV genotype 1b have a higher risk of developing HCC than those infected with other genotypes, [10–14] other studies did not confirm this result [15–18]. As a consequence, no

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consensus has emerged, and the role of HCV genotype in both accelerating the progression of the disease and as a risk factor for HCC remains to be established.

We therefore decided to perform a meta-analysis of published studies, which permitted to evaluate the role of HCV genotype 1b in HCC development with a powerful approach; this enabled us also to assess the sources of inconsistencies and variability in the estimates of the association between HCV genotype 1b and HCC, and to explain whether they may be ascribed to the composition and characteristics of the study population or the methodological features of the performed studies.

2. Materials and methods

Studies suitable for this meta-analysis had to meet the following inclusion criteria: they had to provide either the frequency of HCV genotypes 1b and non-1b in HCC cases and controls or a measure of Relative Risk (RR), with 95% Confidence Intervals (CI), for the association between HCV genotype 1b and HCC development. Papers that reported association for genotype 1 instead of 1b were also included, as they were conducted in countries where 1b was the most common HCV-1 subtype [19–21]. These latter studies were however excluded in sensitivity analyses. Studies based on patients infected with specific HCV genotype(s) were excluded, as well as those on patients who underwent liver transplantation since genotype 1b could be over-represented in patients with decompensated liver disease requiring liver transplantation [20].

We performed a literature search to December 2007 on PubMed, ISI Web of Science (Science Citation Index Expanded) and Embase, using combinations of the keywords "hepatitis C virus", "HCV", "genotype", "hepatocellular carcinoma", "hepatocarcinoma", and "liver cancer". The search was limited to human studies with no language or time restrictions. In addition, we reviewed the references from all retrieved articles and relevant reviews [20–25] to identify additional studies.

After initial screening of abstracts and references, 161 potentially relevant papers were identified and full-text was retrieved for detailed evaluation. Of the 67 papers which met the inclusion criteria, 10 were excluded because they overlapped with other selected papers with larger samples. Of the 57 studies eligible for the meta-analysis, 21 presented adjusted risk estimates for the association between HCV genotype 1b and HCC, while 36 reported only crude data on the frequency of HCV genotypes in cases and controls (Tables 1 and 2).

For each study we recorded information on publication year, study location, study design, period of accrual, type of control, genotype comparison, inclusion and percentage of patients treated with interferon (IFN-α) therapy, with HBV co-infection, or with a history of alcohol abuse, HCC diagnosis, and genotyping methods.

2.1. Statistical analysis

When available, we retrieved adjusted risk estimates presented in the original papers. If not, we retrieved the frequencies of HCV genotypes in cases and controls, and calculated the corresponding study-specific crude Odds Ratio (OR), with 95% CI for HCC risk. We excluded mixed and undetermined genotypes in OR estimation, wherever possible. For studies with zero cells in the two by two table, we calculated OR by adding 0.5 to each of the four cells.

We used random-effects models with the DerSimonian–Laird method [26] to evaluate summary estimate of the overall association of HCV genotype 1b with HCC. Study-specific estimates were weighted by inverse of variance. We ignored the distinction between various measures of RR (i.e. OR and RR) on the assumption that HCC is sufficiently rare [27].

Homogeneity among studies was tested by the Q statistic, with significance level set at 0.10, and by I^2, [28] which represents the percentage of total variation across studies that is attributable to heterogeneity rather than to chance. Between-study heterogeneity was explored through sub-group analyses and meta-regression [29]. We conducted sub-group analyses limited to studies reporting data on HCV genotype 1b (therefore excluding studies that did not differentiate genotype 1b from other HCV-1 subtypes), to studies comparing genotype 1b with type 2, and to studies conducted in subjects with CLD or LC. In order to explore the heterogeneity among studies, we included the following variables in meta-regression: publication year, study location, study design, underlying liver disease, inclusion and percentage of subjects undergoing IFN-α therapy, inclusion and percentage of subjects with HBV co-infection, inclusion and percentage of subjects with history of alcohol abuse, genotyping technique, genotype comparison.

Publication bias was graphically represented by funnel plot and assessed by Egger's test [30].

The statistical analysis was performed using STATA software, version 8.2.

3. Results

We decided to focus the meta-analysis on the 21 studies that presented an age-adjusted estimate for the association between HCV genotype 1b and HCC, or in which cases and controls were matched at least by age. We made this choice since it was argued that the association between genotype 1b and HCC could be, at least partially, explained by a cohort effect: age representing therefore an important confounder. However, in order to check and validate the results based on adjusted risk estimates, we performed an additional analysis on studies providing only crude data: these results were briefly reported and commented.

3.1. Description of the studies

The main characteristics of the 21 studies presenting age-adjusted risk estimates were described in Table 1. The articles were published between 1996 and 2007 and referred to a study period that covered 30 years, from 1976 to 2005. Eleven studies were conducted in Asia, nine in Europe, and one in Australia. Nine were cohort studies, while the remaining 12 were case-control studies. Studies providing frequency of HCV genotypes in prevalent cases, observed in a certain hospital during a specific time period were grouped with the "case-control" studies for the purpose of heterogeneity exploration. Five studies compared HCV genotype frequency in HCC cases and in HCV carriers without a specific CLD (asymptomatic subjects or patients with miscellaneous CLD); the remaining 16 papers focused only on patients with specific CLD: chronic hepatitis (CH) and/or LC. Among these 16 studies, eight articles included data on LC patients, with or without HCC. The laboratory techniques used to identify HCV genotypes varied among studies: PCR with genotype-specific primers was used in 11 studies, HCV Line-Probe-Assay (INNO-LiPA HCV) in six studies or both methods in two studies. In the remaining two papers HCV genotypes were identified by serological tests or by restriction fragment length polymorphisms analysis.