Hepatitis B Virus Gene C1653T Polymorphism Mutation and Hepatocellular Carcinoma Risk: an Updated Meta-analysis

Hua-Ping Shi1,2, Jun Zhang3, Xue-Chai Shang2, Xin-You Xie3*

Abstract

Although there have been many studies investigating possible associations between the C1653T mutation and risk of HCC, the results have been inconsistent. We conducted searches of the published literature in Pubmed and Embase databases up to January 2013. Seventeen studies with a total of 1,085 HCC cases and 1,365 healthy controls were retrieved. We found a significant association between the C1653T mutation and HCC risk (OR = 2.01, 95% CI = 1.49–2.70). In the subgroup analysis by ethnicity, a significant association was also found in Asians (OR = 2.07, 95% CI = 1.71–2.51). In subgroup analysis by HBV genotype, B and C were linked with development of HCC (B: OR = 2.21, 95% CI = 1.13–4.34; C: OR = 2.26, 95% CI = 1.61–3.16). However, no significant association was found between the C1653T mutation and HCC risk in HBsAg positive cases. In conclusion, this meta-analysis suggests that the C1653T mutation may be associated with susceptibility to HCC.

Keywords: HBV - C1653T mutation - HCC - meta-analysis

Introduction

Hepatocellular carcinoma (HCC) is a malignant tumor composed of cells resembling hepatocytes which ranks the sixth most common neoplasm and the third most frequent cause of cancer death (Ferlay et al., 2010). It had an estimated global incidence of more than 500,000 cases in the year 2000, and its incidence is rising in many countries. Most cases of HCC (80%) arise in eastern Asia and sub-Saharan Africa, where the main risk factors for HCC are alcoholism, hepatitis B, hepatitis C, aflatoxin, cirrhosis of the liver, hemochromatosis, Wilson’s disease and type 2 Diabetes (Parkin et al., 2000). However, the most frequent risk factor for HCC is chronic HBV infection, which accounts for more than 50% of all cases (Sherman et al., 2010).

Although a considerable amount of research has been conducted, the molecular basis of HBV-related hepatocarcinogenesis remains unknown (Brechot et al., 2004). Several studies have examined mutations within the HBV genome that may be associated with HCC. HBV contains an incomplete double-stranded DNA genome consisting of four main regions: the PreS/S region (nucleotides or nt 2854–155), the enhancer II (EnhII; nt 1636–1744) region, basal core promoter (BCP, nucleotides 1751–1769) region and the precore region. It has been demonstrated that mutations in the HBV genome which is pertinent to HCC invariably occur at the PreS region, EnhII, BCP and precore region.

The C1653T mutation in the EnhII region of the core promoter that converts histidine at amino acid 94 of the HBx protein to tyrosine (Shinkai et al., 2007; Yuen et al., 2008). Since then, numerous studies have confirmed the association between C1653T mutation and HCC. However, the results have been inconsistent. Up to now, there has been only one published meta-analysis article focusing on the C1653T mutation, and the conclusion is that C1653T is associated with an increased risk of HCC (Liu et al., 2009). With much more studies focusing on the correlation of C1653T mutation with HCC, we update the meta-analysis and produce a subgroup analysis to give a more comprehensive understanding on C1653T mutation with HCC risk.

Materials and Methods

Literature search strategy

We searched Pubmed and Embase databases by two reviewers (Huaping Shi and Xinyou Xie) to retrieve papers linking C1653T polymorphism and HCC risk available by January 2013 without language restrictions, using the following key words: “HBV”, “C1653T”, “liver cancer”, “polymorphism”, “single nucleotide polymorphism”, “genetic polymorphism”, “HCC” and “hepatocellular carcinoma”. The reference lists of major textbooks, reviews, and included articles were identified through manual searches to find other potentially eligible studies. Inclusion and exclusion criteria

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Studies were included in this meta-analysis if they met the following criteria: i) case-control studies that addressed HCC cases and healthy controls; ii) studies that evaluated the association between C1653T polymorphism and HCC risk; and iii) studies that included sufficient data for extraction. Studies were excluded when: i) not case-control studies that evaluated the association between C1653T polymorphism and HCC risk; ii) case reports, letters, reviews, meta-analysis, and editorial articles; iii) studies that were based on incomplete data and those with no usable data reported and duplicate data.

Data extraction
Using a standardized form, data from published studies were extracted independently by two reviewers (Huaping Shi and Xinyou Xie) to populate files with the necessary information. The following information was extracted from each of the included articles: first author, year of publication, country, ethnicity, detection method, number of cases and controls, HBV genotype, and HBeAg status. For conflicting evaluations, agreement was reached following discussion among the authors.

Statistical analysis
Meta-analysis was performed using the STATA package version 12.0 (Stata Corporation, College Station, TX, USA). The strength of the associations between C1653T polymorphism and HCC risk was estimated by odds ratio (OR) and 95% confidence interval (95%CI). Between study heterogeneities were estimated using the F test. F values of 25, 50, and 75% were defined as low, moderate, and high estimates, respectively. When F > 50% indicated heterogeneity across studies, the random effects model was used for meta-analysis, or else the fixed effects model was used. Subgroup analysis based on ethnicity, genotype, and HBeAg were used to explore and explain the diversity among the results of different studies. Sensitivity analysis was mainly performed by sequential omission of individual studies. Publication bias was investigated by Begg’s funnel plot (P < 0.05 was considered statistically significant).

Table 1. Characteristics of the Included Studies for Meta-analysis

<table>
<thead>
<tr>
<th>Study included</th>
<th>Year</th>
<th>Area</th>
<th>Race</th>
<th>Detection method</th>
<th>Mutations /Cases</th>
<th>Mutations /Controls</th>
<th>HBV genotype</th>
<th>HBeAg</th>
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<tbody>
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<td>28 125</td>
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<td>sequence</td>
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<td>15 46</td>
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<tr>
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<td>03 135</td>
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<tr>
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<td>05 69</td>
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<td>sequence</td>
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<td>Asian</td>
<td>PCC</td>
<td>11 20</td>
<td>01 35</td>
<td>B, C</td>
<td>positive</td>
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</table>

Figure 1. Flow Diagram of Study Searching and Selection Process

Results

Studies included in the meta-analysis
The search strategy retrieved 35 potentially relevant studies. Base on the inclusion criteria, only 17 case-control studies (Sakamoto et al., 2006; Tanaka et al., 2006; Shinkai et al., 2007; Wang et al., 2007; Yuan et al., 2007; Zhang et al., 2007; Fang et al., 2008; Guo et al., 2008; Jang et al., 2008; Choi et al., 2009; Ja et al., 2009; Tangkijvanich et al., 2010; Welschinger et al., 2010; Zhu et al., 2010; Cho et al., 2011; Qu et al., 2011; Tatsukawa et al., 2011) with full-text were included in this meta-analysis and 18 studies were excluded. The flow chart of study selection is summarized in Figure 1. These seventeen selected case-control studies included 1085 HCC cases and 1365 healthy controls. All studies were case-control studies that evaluated the association between C1653T mutation and HCC risk. All the articles were written in English. The baseline characteristics of all included studies are summarized in Table 1. Of these studies, sixteen reported on Asians, and one reported on Africans.

Main results, subgroup and sensitivity analysis
A summary of the meta-analysis findings of the association between C1653T mutation and HCC risk is shown in Table 2. Results showed that C1653T correlated with an increased risk of HCC (Figure 2, OR = 2.01, 95%CI = 1.49–2.70). In subgroup analysis by ethnicity,
the C1653T Mutation and HCC Risk

Figure 2. Meta-analysis of the Relationship Between the C1653T Mutation and HCC Risk

The mechanism of how C1653T mutation relates to HCC risk is still unclear. HBx, the nonstructural regulatory protein of HBV, has been strongly associated with the development of liver cancer in some HBx-transgenic mouse strains or with increased progression to liver cancer in other toxin-exposed HBx-transgenic mouse strains. The T1653 mutation resulted in a histidine-tyrosine amino acid substitution at codon 94 of the X protein, which is the center of the immunodominant antigenic domain of amino acids (aa) 85 to 110 (Stemler et al., 2000). These studies suggested that HBeAg-positive C1653T mutation may be one of independent predictive factor for HCC and rapid progress of liver disease compared to genotype B (Chu et al., 2002; Chan et al., 2004). HBeAg positivity and increased progression to liver disease compared to genotype B (Chu et al., 2002; Chan et al., 2004). HBeAg positivity suggests a possible role of ethnic differences in genetic background and the environment in which they lived. Genotypes B and C are found commonly in Asia, and genotype C causes more-serious liver disease than genotype B (Sakurai et al., 2004). In subgroup analysis by HBV genotype, HBV genotype B and C are associated with more severe and rapid progression of liver disease compared to genotype B (Chu et al., 2002; Chan et al., 2004). HBeAg positivity may be one of independent predictive factor for HCC. In the subgroup analysis by HBeAg status, our results suggest that HBeAg-positive C1653T mutation may be not involved with the susceptibility of HCC.

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Discussion

Although several studies have evaluated the association between C1653T mutation and HCC, the association remains poorly understood. Our meta-analysis quantitatively assessed the association between C1653T mutation and susceptibility to HCC. Finally, 17 case-control studies were included and assessed, involving a total of 1085 HCC cases and 1365 healthy controls. The main meta-analysis results showed that significant associations between C1653T mutation and HCC risk. In the subgroup analysis by ethnicity, a significant association was found between C1653T mutation and HCC risk in Asians and no correlation was found in Africans, suggesting a possible role of ethnic differences in genetic backgrounds and the environment in which they lived. Genotypes B and C are found commonly in Asia, and genotype C causes more-serious liver disease than genotype B (Sakurai et al., 2004). In subgroup analysis by HBV genotype, HBV genotype B and C are associated with more severe and rapid progression of liver disease compared to genotype B (Chu et al., 2002; Chan et al., 2004). HBeAg positivity may be one of independent predictive factor for HCC.

In the subgroup analysis by HBeAg status, our results suggest that HBeAg-positive C1653T mutation may be not involved with the susceptibility of HCC.
et al., 1990). Indeed, codon 94 (nt 1653 to 1655) is within the function domain of the X protein, which has been reported to play a central role in transactivation (Kumar et al., 1996). And the C1653T mutation might enhance the binding affinity of related factors and enhancer II/core promoter activity, cause activation of an indolent immune response, as well as abrogates both the antiproliferative and transactivation effects of wild-type HBx (Lee et al., 1998; Sirmah et al., 1999). These changes may be involved in hepatocarcinogenesis.

There were also some limitations in our meta-analysis. First, because of incomplete raw data or publication limitations, some relevant studies could not be included in our analysis. Secondly, the small sample size available was not ideal for detecting small genetic effects. Thirdly, we were not able to address all the sources of heterogeneity that existed among studies, although we could have made subgroup stratifications analysis for the limited number of published studies. Finally, the genotype information stratified for the main confounding variables was not available in the original papers and the confounding factors addressed across the different studies were variable.

In conclusion, the previously reported controversial conclusions on the correlation of C1653T mutation with HCC susceptibility may arise from statistical bias, such as limited sample size or some methodological errors. As suggested by our meta-analysis with a total of 17 eligible studies, C1653T mutation appear to act as an independent risk factor of developing HCC, and further studies are needed to determine its contribution to the genesis of hepatocarcinogenesis.

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References


