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Risk of liver cancer in patients with hepatitis B or C

Key Messages

1. Among hepatitis B virus carriers, infection with genotype C significantly increases the risk of developing hepatocellular cancer compared to those without this genotype.
2. Among hepatitis C virus carriers, infection with genotype 1b increases the risk of hepatocellular cancer two-fold compared to controls without this genotype.
3. Such increased risk should be explained as risk over and above the existing risk associated with each infection.
4. Hepatitis C virus genotypes 1a and 2a are associated with decreased risk of hepatocellular cancer.

Introduction

Hepatitis B and C are common, serious infectious diseases in both developing and developed countries, affecting over one third of the world's population. The prevalence of hepatitis B seropositivity in the adult population of Hong Kong ranges from 4 to 10%.[1] A significant proportion of these subjects develop chronic hepatitis.[2] It is not clear which of these subgroups of the population are at risk of chronic hepatitis and its complications.

Different genotypes of hepatitis B virus (HBV) or hepatitis C virus (HCV) may play a role in determining which groups of the population are at increased risk of developing hepatocellular cancer (HCC).[3,4] The results remain controversial with regard to which genotype is dominant and the magnitude of the increased risk of HCC (if any).[3,4] Knowing which genotype predisposes patients to HCC can help target populations for monitoring and/or early intervention, so as to achieve an early diagnosis and prolong life.

This study aimed to (1) review the literature on HBV/HCV infection and genotypes and their association with HCC, and (2) estimate the magnitude of risk of HCC associated with HBV/HCV infection and different genotypes.

Methods

This study was conducted from January 2004 to July 2005. A comprehensive computerised literature search was conducted in July 2005 from the databases of MEDLINE, PubMed, EMBASE, and CANCERLIT, using various combinations of the terms: hepatitis, hepatitis B, hepatitis C, hepatitis B virus, hepatitis C virus, HBV, HCV, genotype(s), hepatocellular carcinoma, liver neoplasms, liver cancer, incidence, mortality, death rate, epidemiologic studies, case-control study, and cohort study. Links to related citations were also reviewed to identify other potentially relevant studies. To maximise the yield from the literature search, a manually recursive search of relevant articles, the reference list of retrieved articles, and meeting abstracts was also performed.

Studies included were (1) all observational studies (case-control and cohort) that provide age-matched controls, (2) studies with data on genotypes of HBV or HCV in patients with HCC, (3) documented diagnosis of HCC, and (4) all genotyping methods and all languages. Studies without raw data for retrieval as well as duplicate publications were excluded.

Validity of all included studies was critically appraised, according to the guidelines for reading case-control studies.[5] These guidelines entailed (1) an explicit description of the characteristics of cases and controls, how they were selected, and whether they were matched for age, gender, residence, and other factors; (2) information on the detection of HBV/HCV genotypes and how HCC was diagnosed; (3) data collection, analytic methods, sample size; and (4) the quality of data presentation. This assessment process was conducted by two independent reviewers. As the use of quality scoring in meta-analyses is controversial,[6] no score was given during the quality assessment.

Odds ratios (OR) and 95% confidence intervals (CI) of developing HCC in relation to genotypes of HBV/HCV infection were calculated using either a

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fixed- or random-effects model, depending on the result of homogeneity tests. Between-study heterogeneity was tested using the Cochran method. A p value of <0.1 was considered statistically significant for the test of homogeneity.

Results

A total of 869 potentially relevant citations were generated; 83 studies were included.

Hepatitis B virus genotypes and risk of hepatocellular cancer

There were 20 case-control and 4 cohort studies (involving 865 cases of HCC and 5858 controls) to provide raw data on the association between HBV genotypes and the risk of developing HCC.

Regarding the HBV genotype A and HCC, 16 case-control and one cohort studies (involving 739 cases and 5002 controls) were analysed. The prevalence of genotype A was 4.74% (35/739) among cases and 5.74% (287/5002) among controls, yielding an OR of 1.29 (95% CI, 0.84-1.97). The test of homogeneity was non-significant (Q Cochran=13.94, df=16, p=0.60). This suggested that patients harbouring HBV genotype A did not confer significant additional risk of developing HCC compared to those carrying HBV alone.

Regarding the HBV genotype B and HCC, 18 case-control and three cohort studies (involving 825 cases and 5426 controls) were analysed. The prevalence of genotype B was 24.6% (203/825) among cases and 25.9% (1406/5426) among controls, yielding an OR of 0.62 (95% CI, 0.45-0.86). This suggested that patients infected with HBV genotype B were at reduced risk of developing HCC compared to those without this genotype.

Regarding the HBV genotype C and HCC, 18 case-control and three cohort studies (involving 825 cases and 5426 controls) were analysed. The prevalence of genotype C was 64.6% (533/825) among cases and 66.7% (3618/5426) among controls, yielding an OR of 1.37 (95% CI, 1.12-1.68). This indicated that patients harbouring HBV genotype C were at increased risk of developing HCC compared to those without this genotype.

Regarding the HBV genotype D and HCC, 11 case-control and one cohort studies (involving 443 cases and 2218 controls) were analysed. The prevalence of HBV genotype D was 9.5% (42/443) among cases and 17.99% (399/2218) among controls, yielding an OR of 0.74 (95% CI, 0.31-1.79). This suggested that HBV genotype D was not related to the development of HCC.

Hepatitis C virus genotypes and risk of hepatocellular cancer

There were 46 case-control and 13 cohort studies (involving 2000 cases of HCC and 10 974 controls) to provide raw data on the association between HCV genotypes and the risk of developing HCC.

Regarding the HCV genotype 1 and HCC, six case-control and three cohort studies (involving 153 HCC cases and 1249) controls were analysed. The prevalence of HCV genotype 1 was 15.0% (23/153) among cases and 39.3% (491/1249) among controls, yielding an OR of 0.77 (95% CI, 0.43-1.40).

Regarding the HCV genotype 1a and HCC, 32 case-control and six cohort studies (involving 1317 cases and 7116 controls) were analysed. The prevalence of HCV genotype 1a was 3.6% (47/1317) among cases and 6.7% (478/7116) among controls, yielding an OR of 0.53 (95% CI, 0.38-0.75). This suggested that patients harbouring the HCV genotype 1a had a significantly lower risk of developing HCC compared to those without this genotype.

Regarding the HCV genotype 1b and HCC, 44 case-control and 11 cohort studies (involving 1962 cases and 10291 controls) were analysed. The prevalence of HCV genotype 1b was 72.3% (1419/1962) among cases and 59.4% (6133/10291) among controls, yielding an OR of 1.97 (95% CI, 1.63-2.37). This suggested that the HCV genotype 1b was associated with a significantly increased risk of developing HCC.

Regarding the HCV genotype 2 and HCC, nine case-control and five cohort studies (involving 185 cases and 1809 controls) were analysed. The prevalence of HCV genotype 2 was 10.6% (44/417) among cases and 10.2% (185/1809) among controls, yielding an OR of 0.721 (95% CI, 0.47-1.096).

Regarding the HCV genotype 2a and HCC, 29 case-control and five cohort studies (involving 1276 cases and 7193 controls) were analysed. The prevalence of HCV genotype 2a was 12.1% (127/1053) among cases and 17.7% (1276/7193) among controls, yielding an OR of 0.78 (95% CI, 0.63-0.96).

Regarding the HCV genotype 2b and HCC, 26 case-control and four cohort studies (involving 275 cases and 5727 controls) were analysed. The prevalence of HCV genotype 2b was 2.9% (34/1174) among cases and 4.8% (275/5731) among controls, yielding an OR of 0.92 (95% CI, 0.67-1.39).

Discussion

Only a minority of patients with HBV or HCV infection develop HCC, despite the high prevalence of such infection. Identifying different genotypes of HBV/HCV helps explain why some patients are prone to developing HCC. No quantitative systematic review of the association between HBV/HCV genotypes and HCC has been published.

Although eight HBV genotypes have been identified, only data for genotypes A to D were adequate for a meaningful meta-analysis. For HBV genotype A, no significantly difference in the sero-frequency was noted. This suggested that genotype A was not common among patients with HBV infection, and not associated with the development of HCC. It neither increased nor decreased the risk of HCC among HBV carriers. For HBV genotypes B and D, they were also not associated with the development of HCC. Patients with HBV genotype C were at increased risk of developing HCC compared to those without this genotype. As HBV genotype C is most commonly found in South East Asia, where the prevalence of HCC is high, the magnitude of risk of developing HCC might have been underestimated due to a high background prevalence of HBV genotype C in HBV carriers without HCC. Therefore, the observed risk ratio of 1.37 should be explained as the risk for HCC over and above any existing risk associated with HBV infection.

The prevalence of HCV infection has increased in the last two decades as a result of increasing rates of drug abuse and transfusion of contaminated blood and blood products. Among HCV-infected patients, only 3.6% of the HCC patients and 6.7% of the controls were sero-positive for genotype 1a. Therefore, the clinical importance of HCV genotype 1a in relation to HCC is unclear. Further studies are needed to examine the clinical importance of this finding. For patients with HCV genotype 1b, they were at increased risk (nearly two-fold) of developing HCC than those without this genotype. A significantly decreased risk ratio was observed for HCV genotype 2a, but not for HCV genotypes 2 and 2b, suggesting that genotypes 2 and 2b had a lesser role, if any, in the development of HCC among HCV-infected patients.

There were several limitations to the current meta-analysis. We focused on individual genotypes and did not take into consideration that patients could have been infected with both HBV and HCV or multiple genotypes. We intentionally broadened the inclusion criteria to maximise the generalisibility of study results. However, cases and controls might not have had comparable durations of infection, which is one of the prognostic factors for HCC development. It is not adequate to examine just one risk factor using multivariate analysis, as HCC is a multi-factorial disease. Although we initially aimed to examine correlations between HBV/HCV genotypes and the incidence and mortality of HCC, the necessary information was not available.

Conclusions

Conflicting reports on the association between these genotypes and HCC make it difficult for clinicians to select which patients to monitor or intervene to prevent the development of HCC. We nevertheless conclude that (1) among HBV carriers, infection with genotype C significantly increases the risk of developing HCC compared to those without this genotype; (2) among HCV carriers, infection with genotype 1b increases the risk of HCC two-fold compared to controls without this genotype; (3) such increased risk should be explained as risk over and above the existing risk associated with HBV or HCV infection; and (4) HCV genotypes 1a and 2a are associated with a decreased risk of developing HCC. However, the clinical importance of these findings remain to be determined.

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