A Population-Based Study of Hepatitis D Virus as Potential Risk Factor for Hepatocellular Carcinoma

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Hepatitis D virus (HDV) is dependent on the presence of hepatitis B virus (HBV) for transmission and replication because of its inability to produce its own coat. It remains uncertain whether HDV infection increases the risk of hepatocellular carcinoma. Using the Swedish Hospital Discharge Register and Outpatient Registry, we identified 9160 patients with chronic HBV infection between 1997 and 2008, of whom 327 had chronic HDV infection and 323 had acute HDV infection. Standardized incidence ratios (SIRs) were calculated for these patients compared with the general population. The risk of hepatocellular carcinoma was greatly increased in patients with HBV and HDV (SIR = 137.17, 95% confidence interval [CI] = 62.19 to 261.51). The risk of hepatocellular carcinoma among patients with HBV and HDV was increased (SIR = 6.11, 95% CI = 2.77 to 11.65) when patients with chronic HBV infection alone were used as the reference population. Similar results were observed for patients with chronic HDV infection (SIR = 99.26, 95% CI = 42.39 to 196.55). Our findings indicate that HDV is a strong risk factor for hepatocellular carcinoma.

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Hepatitis D virus (HDV), one of five known hepatitis viruses, is dependent on hepatitis B virus (HBV) for its transmission and replication because of its inability to produce its own coat (1,2). The prevalence of HDV infection is lower in Northern Europe and North America compared with Eastern Europe, Mediterranean countries, and Western Asia (3). In total, around 5% of hepatitis B surface antigen carriers worldwide are infected with HDV (3). Coinfection with HDV and HBV, or HDV superinfection (ie, HDV infects the cells which were previously infected by HBV) among individuals with chronic HBV, can lead to acute or chronic delta hepatitis (4). Several studies have shown that infection with HDV in combination with HBV leads to more severe chronic hepatitis and cirrhosis compared with infection with HBV alone (1,2,5). However, it remains unclear whether HDV infection increases the risk of hepatocellular carcinoma, as it was defined as being “not classifiable to carcinogenicity to humans” in an International Agency for Research on Cancer monograph (1,2).

We used the Swedish Hospital Discharge Register and Outpatient Registry to identify individuals diagnosed in hospitals or outpatient clinics with HBV infection with or without HDV between January 1, 1997, and December 31, 2008. The Swedish Hospital Discharge Register was founded in the year 1964 by the National Board of Health and Welfare and has had complete nationwide coverage since 1987. Outpatient data have been recorded since the year 2000. Patients were identified according to the Tenth Revision of the International Classification of Diseases using the following codes: B181 (chronic HBV infection without HDV), B180 (chronic HBV infection with HDV), and B171 (acute HDV infection in HBV carriers). We further linked these patients to the Swedish Cancer Registry to identify all incident cancers during the study period. Founded in the year 1958, the Swedish Cancer Registry is maintained by the National Board of Health and Welfare and has close to 100% coverage at the present time. ICD-7 code 155 and histological code 066 were used to identify patients with hepatocellular carcinoma. Only the first primary cancer for each patient was included in the analysis, thus excluding metastatic cancers. In Sweden, all newly diagnosed cancers must be recorded in the Cancer Registry (6). Additional linkages were made to the Swedish National Population and Housing Census to obtain information on individual-level socioeconomic status, to the Cause of Death Register to identify the date of death, and to the Emigration Registry to identify the date of emigration. All linkages were performed using individual national identification numbers, which were replaced with serial numbers to preserve patient anonymity.

Person-years of risk were calculated from the date of birth or immigration, or January 1, 1961 (whichever came last), until the diagnosis of cancer, death, emigration, or the end of the study period (whichever came first). In model A of Table 1, the reference group was the total population in Sweden with an age-adjusted incidence rate (world standard population) of 1.3/100,000 person-years; in model B, the reference group was those patients with only HBV infection with an age-adjusted incidence rate of 5.51/100,000 person-years. Standardized incidence ratios were calculated as the ratio of the observed and expected numbers of cancers (7,8). The expected number of cancers was calculated by the incidence rates in the reference groups and adjusted by 5-year age group, sex (male or female), 5-year period for the date of diagnosis, socioeconomic status (farmer, self-employed, manual worker, white-collar worker, professional, and other), and residential area (large cities, southern, and northern Sweden) (9). For the standardized incidence ratios (SIRs), 95% confidence intervals (CIs) were calculated assuming a Poisson distribution (9). Hazard ratios were calculated using Cox regression for comparison with the standardized incidence ratio. The proportional hazards assumption was tested by Schoenfeld residuals and by plotting the log of the negative
log of the survival function vs the log of time. All analyses were performed using SAS statistical software (version 9.1; SAS Institute, Cary, NC). The study was approved by the Ethics Committee at Lund University, Sweden.

After excluding those coinfected with hepatitis C virus and HIV, a total of 9160 patients were identified with chronic HBV infection during the study period. The median age at diagnosis was 34 years with a male/female ratio of 1.07, and 83.6% of patients were immigrants from HBV high-prevalence countries. Among the 9160 patients, 327 were diagnosed with chronic HDV infection and 323 with acute HDV infection. Compared with the general population (Table 1), the standardized incidence ratios for hepatocellular carcinoma among patients with acute and chronic HDV infections were high (SIR = 137.17, 95% CI = 62.19 to 261.51 vs SIR = 99.26, 95% CI = 42.39 to 196.55, respectively). Using patients with HBV infection alone as the reference group, the standardized incidence ratios remained high (SIR = 6.11, 95% CI = 2.77 to 1.65 vs SIR = 3.90, 95% CI = 1.61 to 7.22, respectively), indicating that the increased standardized incidence ratio of hepatocellular carcinoma in HDV patients was independent of HBV infection. Compared with patients with HBV infection alone, Cox regression analyses showed that the hazard ratios (HRs) of developing hepatocellular carcinoma were high (HR = 3.85, 95% CI = 1.87 to 7.89 vs HR = 2.42, 95% CI = 1.29 to 4.56 for patients with acute and chronic HDV infection, respectively). We further examined the risk of hepatocellular carcinoma by sex and birth country (Table 2). The standardized incidence ratios of hepatocellular carcinoma were higher in male patients (SIR = 175.81, 95% CI = 75.08 to 348.11 for patients with acute HDV infection; SIR = 115.64, 95% CI = 45.84 to 239.61 for patients with chronic HDV infection, respectively) compared with female patients (SIR = 49.73, 95% CI = 0.02 to 285.06 for patients with acute HDV infection; SIR = 49.84, 95% CI = 0.02 to 285.72 for patients with chronic HDV infection).

The major strengths of our study include the analysis of a relatively large number of patients from a national population. The use of a nationwide database covering the entire population avoided selection bias. Also, patients diagnosed with hepatitis C virus and HIV were eliminated, thus excluding potential confounding effects of hepatitis C virus and HIV status.

One limitation of this study is that the information about individual risk factors, such as alcohol use and aflatoxin B1 intake, was lacking in our database. However, the relatively high risk of hepatocellular carcinoma observed in our study could not be confounded by other known risk factors because the relative risk of hepatocellular carcinoma caused by other risk factors, such as alcohol intake and aflatoxin B1 consumption, was lower than the relative risk observed in this study. Another limitation is that HDV infection was retrieved from the Swedish Hospital Discharge Registry, thus, we could not control for the accuracy of the diagnosis. However, a recent external review suggested that the overall accuracy of the Swedish Hospital Discharge Registry is approximately 85%–95% (10).

In summary, our data suggest that HDV infection is a strong risk factor for hepatocellular carcinoma. The incidence of hepatocellular carcinoma was somewhat higher in patients with acute HDV infection compared with those patients with chronic infection, and it was more prominent in male patients and patients who had immigrated from other countries. The carcinogenic effect of HDV could be related to the increased risk of cirrhosis, a strong risk factor for liver cancer (11). Findings supporting this hypothesis have been previously reported (2) but came from analyses using patients with HBV infection alone.

### Table 1. Risk of hepatocellular carcinoma in patients diagnosed with hepatitis B virus (HBV) infection (n = 9160) together with or without hepatitis D virus (HDV) *

<table>
<thead>
<tr>
<th>Patients</th>
<th>No. of patients</th>
<th>Person-years of follow-up</th>
<th>Model A</th>
<th>Model B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>O</td>
<td>E</td>
<td>SIR (95% CI)†</td>
<td>O</td>
</tr>
<tr>
<td>HBV with acute HDV infection</td>
<td>323</td>
<td>8659</td>
<td>0.07 137.17 (62.19 to 261.51)</td>
<td>9</td>
</tr>
<tr>
<td>HBV with chronic HDV infection</td>
<td>327</td>
<td>7178</td>
<td>8 0.08 99.26 (42.39 to 196.55)</td>
<td>8</td>
</tr>
<tr>
<td>HBV without HDV infection</td>
<td>8510</td>
<td>153974</td>
<td>46 1.71 26.90 (19.46 to 36.26)</td>
<td></td>
</tr>
</tbody>
</table>

* Data under model A were calculated using the general population as the reference, whereas data under model B used patients with HBV infection and without HDV as the reference. CI = confidence interval; E = expected number of cancers, and calculated by the incidence rates in the reference groups; NA = not applicable; O = observed number of cancers; SIR = standardized incidence ratio.
† SIRs were adjusted for age (5-year age group), sex (male or female), 5-year period for the date of diagnosis, socioeconomic status (farmer, self-employed, manual worker, white-collar worker, professional, and other), and residential area (large cities, southern, and northern Sweden).
of data from a total of 39 patients with cirrhosis and HDV infection, so larger studies of the association are needed.

References


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Notes

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