Hepatocellular Carcinoma and Other Liver Disease Among Greenlanders Chronically Infected with Hepatitis B Virus: A Population-Based Study

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Background
In Greenland, the prevalence of hepatitis B surface antigen carriers, reflecting chronic hepatitis B virus (HBV) infection, is 5%–10%. However, the incidence of cirrhosis and hepatocellular carcinoma in this population has been reported to be low. We investigated this discrepancy in a large population-based cohort study.

Methods
In total, 8879 Greenlanders (16% of the population) were recruited for population-based surveys performed from May 5 to July 7, 1987, and from November 1 to November 21, 1998, with follow-up until March 31, 2010. HBV status was based on serological testing, supplemented by data from all available HBV registries in Greenland to determine changes in HBV status over time. Information on morbidity and mortality was obtained from the Patient Discharge Registry, the Cancer Registry, and the Central Registration System. Sex, age, ethnicity, and period-adjusted incidence rate ratios (IRRs) were estimated using Poisson regression. World standardized rates were derived from these and World Health Organization data.

Results
The 650 chronically HBV-infected persons had higher rates of hepatocellular carcinoma (adjusted IRR = 8.70; 95% CI = 2.06 to 36.7), liver disease (adjusted IRR = 5.73, 95% CI = 3.52 to 9.34), and all-cause mortality (adjusted IRR = 1.47; 95% CI = 1.21 to 1.79) than the 5160 HBV-negative persons. However, the world standardized incidence rates of hepatocellular carcinoma (38.5 cancers per 100,000 person-years) and cirrhosis (24 cases per 100,000 person-years) among chronically HBV-infected persons were low compared with results from population-based studies from countries with low, intermediate, and high rates of endemic HBV infection.

Conclusion
The relatively low incidence of hepatocellular carcinoma and other HBV-related morbidity among chronic HBV-infected persons in Greenland suggest a more benign course of HBV among the Greenlandic Inuit than in populations in other parts of the world.

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Worldwide, Hepatitis B virus (HBV) infection is a major health problem. Approximately one-third of people worldwide have positive serological markers of current or previous infection. It is estimated that 350 million persons worldwide are hepatitis B surface antigen (HBsAg)–positive, reflecting chronic HBV infection (1). HBV infection is known to cause acute and chronic hepatitis, cirrhosis, and hepatocellular carcinoma (2), and population-based studies have shown increased rates of liver disease–related mortality among HBV-infected persons (3–5). However, the burden of HBV-related disease has never been measured by hospitalizations in a population-based setting.

Cross-sectional studies of HBV prevalence in Greenland have estimated that approximately 40%–45% of people there are Hepatitis B core antibody (anti-HBc)–positive and 5%–10% are HBsAg-positive (6–8). Despite the high rate of chronic HBV infection in Greenland, cirrhosis and hepatocellular carcinoma have been reported less frequently than expected. Compared with hepatocellular carcinoma incidence rates in men and women in Denmark, where endemic HBV infection rates are low and the HBsAg prevalence is below 0.1% (9), the incidence of hepatocellular carcinoma in men in Greenland from 1969 to 1997 was only twofold greater, and the rate in women was not substantially different (10,11). Likewise, the incidence of liver cirrhosis in Greenland and Denmark are similar (12,13). It should be noted, however, that the studies that found low risks of liver disease among Greenlanders were all published before the reporting of hospital discharge diagnoses to the Greenlandic Discharge Registry became mandatory. Furthermore, the studies were all ecologic, that is, they compared contemporary prevalence of HBV infection, cirrhosis, and hepatocellular carcinoma in the Greenlandic population without studying the relationship between HBV infection and liver disease in the same individuals.

Because of the apparently low frequency of long-term consequences, HBV vaccination was not a part of the childhood...
vaccination program in Greenland until September 1, 2010, when universal HBV vaccination of newborns was initiated. From January 1, 1992, however, it has been Greenlandic policy to screen all pregnant women for HBsAg and to vaccinate all infants of HBsAg-positive mothers.

We carried out a population-based longitudinal cohort study of sequelae to HBV infection in a large Greenlandic cohort that included 16% of the population. Participants were characterized with regard to HBV status in the initial surveys in 1987 and 1998, with follow-up until March 31, 2010.

Subjects and Methods

Greenland is an island with 16 towns and approximately 60 settlements, all located along the coast. Of the 56,000 inhabitants, 85% are Greenlandic Inuit and 15% are non-Inuit (mostly Danes). The Civil Registration System (CRS) includes all persons who have lived in Greenland at some point since June 1, 1972, and/or in Denmark at some point since April 2, 1968 (14); all such residents have been assigned a unique personal identification number (CRS number). The CRS number is used for all administrative purposes and can therefore be used to link information from Greenlandic and Danish national registers. The CRS is continuously updated and contains information on date and place of birth, sex, current and past addresses, parents, and date of death or emigration. In this study, we defined Inuit ethnicity as having two parents born in Greenland; if the father was not identified, ethnicity was based on the maternal birthplace only.

The study cohort consisted of persons who participated in one of two serological surveys, conducted from May 5 to July 7, 1987, and from November 1 to 21, 1998, respectively. The 1987 serological survey was a population-based survey to screen for syphilis in two districts in western Greenland (Asiaat and Maniitsoq) and four districts in southern Greenland (Nanortalik, Qaqortoq, Narsaq, and Paamiut). Of 14,006 randomly selected persons aged 15–70 years, 7,609 (54%) participated (15). Sera from 6267 persons remained available. The 1998 serological survey was a population-based HIV prevalence screening survey in the Sisimiut district in western Greenland (16). The study population included all persons in the district who were older than 5 years of age, and participation patterns were similar to those in the 1987 survey. Of 4807 eligible participants, 2858 (59%) participated and sera from 2800 persons were available. Eighty-four persons participated in both surveys.

In 2007, vital status and current addresses for all participants in the 1987 and 1998 serological surveys were retrieved from the CRS. All persons from the 1987 serological survey who were alive on March 1, 2007, received a letter with information about this study that allowed them the chance to decline to have their stored serum tested for HBV; consent to participate was assumed unless subjects refused. Participants from the 1998 survey had already given written consent for unspecified future analyses of their stored serum. In total, 1,126 persons who died before November 1, 2007, had their serum tested for HBV on the authority of the Greenlandic Commission for Scientific Research.

Stored serum samples from both previous serological surveys were tested for HBV markers in the Department of Virology at Statens Serum Institut (Copenhagen, Denmark) using micro particle enzyme immunoassay (MEIA) kits (Abbott, Wiesbaden, Germany). All samples were first tested for anti-HBc; when positive, samples were also tested for HBsAg.

Assessment of HBV Status

Based on anti-HBc and HBsAg test results, HBV status was defined as chronic (anti-HBc and HBsAg positive), immune (anti-HBc positive and HBsAg negative), or HBV negative (anti-HBc negative). We supplemented the HBV results from the participants with information from all available registers of HBV results in Greenland, in order to learn about changes in the participants’ HBV status over time. The HBV Incidence Notification Register (January 8, 1987, to December 1, 1993) included all new HBV infections that were voluntarily reported by Greenlandic hospitals to the Chief Medical Officer. The Greenlandic Hepatitis B Database (HB database), which has operated from January 1, 1992, to the present, records the results of all HBV testing in Greenland, which is performed at Queen Ingrid’s Hospital, Nuuk (the capital of Greenland) using MEIA (Abbott, Wiesbaden, Germany). Finally, a follow-up study was conducted of all individuals with chronic HBV infection from both previous serological surveys; all chronically HBV-infected persons who were alive on November 1, 2007, were frequency-matched 1:1.5 by age, sex, and district with HBV-immune and HBV-negative persons randomly drawn from their original cohorts. Blood was drawn from participants between
March 1, 2008, and December 10, 2009, and testing for anti-HBc and HBsAg (for anti-HBc positives only) was conducted in the Department of Virology at Statens Serum Institut (Copenhagen, Denmark) from March 21, 2008, to January 15, 2010. The samples were stored at −80°C until tested. Thus, during follow-up, a person in our cohort could change HBV status if a new HBV test result was registered in any of the three above mentioned sources; such persons were recategorized according to their new status beginning on the date of the new test result.

Ethical Approval
The study complied with the Helsinki Declaration II and required informed consent from study participants. The study was approved by the Commission for Scientific Research in Greenland, which acts as a scientific ethics committee for Greenland, and the Danish Data Protection Agency.

Assessment of Morbidity and Mortality
The participants were linked to nationwide morbidity registries by personal identity number. Data on hospitalizations between January 1, 1987 and, March 31, 2009, were retrieved from the Greenlandic and Danish Hospital Discharge Registries (17). The Danish Hospital Discharge Registry (DHDR) is a nationwide register of all hospital discharge diagnoses from January 1, 1977, to the present (17). An in-depth validation study has reported good consistency between medical records and the diagnoses reported in the register (18). The Greenlandic Hospital Discharge Registry (GHDR) is constructed in the same way as its Danish counterpart; recording of all discharge diagnoses in the register has been mandatory since January 1, 1987. Selected groups of diagnoses that could be associated with HBV infection or liver disease, as well as potential confounding conditions, were chosen for study. Conditions were categorized based on International Classification of Diseases (ICD)-8 (January 1, 1987, to December 31, 1993) and ICD-10 (January 1, 1994, to March, 31, 2009) codes (see table footnotes).

The Danish Cancer Registry contains information on incident cancers diagnosed in Denmark since January 1, 1943, based on notifications from hospital departments and specialists as well as autopsy reports from the Danish Pathology Registry. Cancers from Greenland have been included in the register since 1963, and the registration of cancers in Greenlanders diagnosed in Greenland has been mandatory since 1987 (19,20). The registry consists of notifications from physicians diagnosing and treating cancer patients, supplemented by pathological reports and death certificates. The validity and completeness of the registry have previously been evaluated, and the data are considered to be of high quality (19,20). Cancers diagnoses were based on information from both the Danish Cancer Registry (primary source) and the Greenlandic and Danish Hospital Discharge Registries. All-cause mortality was obtained based on information on vital status from the CRS from January 1, 1987, to March 31, 2010.

Statistical Analyses
Incidence rate ratios (IRRs) for morbidity and all-cause mortality by HBV status were estimated using log-linear Poisson regression, with the logarithm of person-years as the offset, adjusted for sex, age, ethnicity (Inuit, mixed and non-Inuit), and period. Adjustments for age and period were made using cubic splines constrained to be linear in the tails, with knots at the 5th, 35th, 65th, and 95th percentiles for each disease (21). For each endpoint (morbidity due to specific causes and all-cause mortality), follow-up started on the date of the first HBV test in any of the above mentioned databases (see “Assessment of HBV Status”) or January 1, 1987, whichever came later. Follow-up ended at first diagnosis of the endpoint of interest, death, emigration, or December 31, 2008, whichever came first, and for all-cause mortality follow-up ended at death, emigration, or March 31, 2010, whichever came first. HBV status was treated as a time-dependent variable. Effect modification by age and sex was evaluated by inclusion of interaction terms in the regression model. Furthermore, as a check on our model, we evaluated whether the age effect for liver disease and all-cause mortality differed between the 1987 and the 1998 cohorts and found no difference. Incidence rates standardized to the world population, for brevity referred to hereafter as world standardized rates, were estimated using age-specific incidence rates from our study and the World Health Organization’s world standard population distribution (22). Associations with two-sided P-values less than .05 were considered to be statistically significant. Analyses were performed using SAS, version 9.2 (SAS Institute Inc, Cary, NC).

Results
Participants
Of 8983 potential participants, 104 (1.2%) were excluded; of these, 46 were excluded at their request and 58 were excluded because of an invalid CRS number in the original files. Thus, we retrieved morbidity information from the registers for 8879 persons who had an HBV test result recorded in the original serological surveys. This cohort was followed for 151 192 person-years with a median follow-up of 22.8 years, and 84.5% of the participants were followed to the end of study (March 31, 2010). When we examined demographic characteristics of the study participants by HBV status at the first test, of the 8879 samples tested, 650 (7.3%) were HBsAg-positive and 3069 (34.6%) were anti-HBc positive, but HBsAg negative (categorized as HBV immune) (Table 1). HBsAg and anti-HBc positivity were more frequent among Inuit (7.8% and 37.4%, respectively) than among non-Inuit, who were mostly Danes (1.3% and 10.7%, respectively) (Table 1). There were 5160 (58.1%) HBV-negative individuals in this cohort.

Morbidity
First, we calculated age-, sex-, ethnicity-, and period-adjusted IRRs for first hospital admission with selected diagnoses by HBV status (Table 2). The rate of liver disease overall was 5.73 times higher for chronically HBV-infected persons (adjusted IRR = 5.73, 95% CI = 3.52 to 9.34) than for HBV-negative persons. Hospital admissions for cirrhosis, chronic nonalcoholic hepatitis, and acute hepatitis were 4.52, 11.0, and 14.0 times more common, respectively, among chronically HBV-infected persons than among HBV-negative persons. By contrast, hospital admissions due to alcoholism, alcohol-related liver diseases (alcohol-induced chronic hepatitis and cirrhosis), and HIV infection did not differ statistically significantly among chronically HBV-infected, HBV-immune,
and HBV-negative persons. However, chronically HBV-infected and HBV-immune persons had statistically significantly increased risks of admission because of tuberculosis and ulcers, respectively, compared with HBV-negative persons. Among chronically HBV-infected persons, the world standardized rates of liver disease overall, nonalcoholic chronic hepatitis, and nonalcoholic cirrhosis were 525 cases per 100 000 person-years, 111 cases per 100 000 person-years, and 24 cases per 100 000 person-years, respectively. The

### Table 1. Characteristics by hepatitis B Virus (HBV) status at the time of the first test (in 1987 or 1998)*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All subjects</th>
<th>Chronically HBV infected (HBsAg+)</th>
<th>HBV-immune † (HBsAg− and HBcAb+)</th>
<th>HBV negative (HBcAb−)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number tested, No. (%)</td>
<td>8879</td>
<td>660 (7.3%)</td>
<td>3069 (34.6%)</td>
<td>5160 (58.1%)</td>
</tr>
<tr>
<td>Cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1987 cohort, No. (%)</td>
<td>6170 (100)</td>
<td>478 (7.8)</td>
<td>2319 (37.6)</td>
<td>3373 (54.7)</td>
</tr>
<tr>
<td>1998 cohort, No. (%)</td>
<td>2709 (100)</td>
<td>172 (6.4)</td>
<td>750 (27.7)</td>
<td>1787 (66.0)</td>
</tr>
<tr>
<td>Age at testing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean, y (SD)</td>
<td>30.5 (14.4)</td>
<td>33.4 (12.4)</td>
<td>35.6 (13.4)</td>
<td>27.1 (14.2)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>4390 (100)</td>
<td>359 (8.2)</td>
<td>1440 (32.8)</td>
<td>2591 (59.0)</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>4489 (100)</td>
<td>291 (6.5)</td>
<td>1629 (36.3)</td>
<td>2569 (57.2)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inuit, No. (%)</td>
<td>7874 (100)</td>
<td>625 (7.9)</td>
<td>2944 (37.4)</td>
<td>4305 (54.7)</td>
</tr>
<tr>
<td>Mixed, No. (%)</td>
<td>346 (100)</td>
<td>12 (3.5)</td>
<td>47 (13.6)</td>
<td>287 (83.0)</td>
</tr>
<tr>
<td>Non-Inuit, No. (%)</td>
<td>620 (100)</td>
<td>8 (1.3)</td>
<td>66 (10.7)</td>
<td>546 (88.1)</td>
</tr>
<tr>
<td>Unknown, No. (%)</td>
<td>39 (100)</td>
<td>5 (12.8)</td>
<td>12 (30.8)</td>
<td>22 (56.4)</td>
</tr>
</tbody>
</table>

* HBsAg = Hepatitis B surface antigen; HBcAb = Hepatitis B core antibody; SD = standard deviation; − = negative, + = positive.
† The immune group included 477 (5.4%) persons who were HBcAb positive, but further characterization was not possible due to either insufficient serum or an inconclusive HBsAg test result. These persons were classified as immune.

### Table 2. Incidence rate ratios (IRRs) for hospitalization by hepatitis B Virus (HBV) status in a population-based cohort of 8879 persons in Greenland*

<table>
<thead>
<tr>
<th>Hospitalizations†</th>
<th>All</th>
<th>Chronically HBV-infected (HBsAg+)</th>
<th>HBV-immune † (HBsAg− and HBcAb+)</th>
<th>HBV negative (HBcAb−)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case patients</td>
<td>Case patients</td>
<td>Adjusted IRR (95% CI)$§</td>
<td>Case patients</td>
<td>Adjusted IRR (95% CI)$§</td>
</tr>
<tr>
<td>All liver-related diseases</td>
<td>117</td>
<td>31</td>
<td>5.73 (3.52 to 9.34)</td>
<td>45</td>
</tr>
<tr>
<td>Chronic nonalcoholic liver diseases</td>
<td>56</td>
<td>21</td>
<td>10.8 (5.34 to 22.0)</td>
<td>21</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>17</td>
<td>4</td>
<td>4.52 (1.23 to 16.7)</td>
<td>6</td>
</tr>
<tr>
<td>Chronic hepatitis</td>
<td>47</td>
<td>18</td>
<td>11.0 (5.13 to 23.6)</td>
<td>17</td>
</tr>
<tr>
<td>Acute hepatitis</td>
<td>17</td>
<td>9</td>
<td>14.4 (4.49 to 43.9)</td>
<td>2</td>
</tr>
<tr>
<td>Other liver-related diseases</td>
<td>20</td>
<td>0</td>
<td>NE</td>
<td>11</td>
</tr>
<tr>
<td>Alcoholic liver diseases</td>
<td>24</td>
<td>1</td>
<td>0.51 (0.07 to 3.99)</td>
<td>8</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>618</td>
<td>52</td>
<td>1.12 (0.83 to 1.51)</td>
<td>245</td>
</tr>
<tr>
<td>Pancreatic diseases</td>
<td>58</td>
<td>3</td>
<td>0.87 (0.26 to 2.94)</td>
<td>30</td>
</tr>
<tr>
<td>Uterus</td>
<td>541</td>
<td>50</td>
<td>1.35 (0.99 to 1.83)</td>
<td>262</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>242</td>
<td>28</td>
<td>1.64 (1.08 to 2.50)</td>
<td>111</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>120</td>
<td>2</td>
<td>0.23 (0.06 to 0.96)</td>
<td>55</td>
</tr>
<tr>
<td>HIV</td>
<td>11</td>
<td>0</td>
<td>NE</td>
<td>5</td>
</tr>
</tbody>
</table>

* HBcAb = Hepatitis B core antibody; HBsAg = Hepatitis B surface antigen; SD = standard deviation; − = negative, + = positive.
‡ The immune group included 477 (5.4%) persons who were HBcAb positive, but further characterization was not possible due to either insufficient serum or an inconclusive HBsAg test result. These persons were classified as immune.
§ For each individual, person-years were calculated from the time of the first HBV test result in any database or January 1, 1987, whichever came later, until the date of diagnosis, death, emigration or December 31, 2008, whichever came first. The model was adjusted for age (splines), sex, period (splines), and ethnicity. The IRRs were computed using the HBV-negative group as the reference group.
sex- and age-specific mortality rates per 100 000 person-years for chronic liver diseases are higher among chronically HBV-infected Greenlanders than HBV-negative Greenlanders (Figure 1).

Next, we calculated IRRs for cancer diagnoses by HBV status (Table 3). Compared with HBV-negative persons, the rate of hepatocellular carcinoma was 8.70 times higher for chronically HBV-infected persons (adjusted IRR = 8.70; 95% CI = 2.06 to 36.7) and two times higher for HBV-immune persons. The world standardized rate of hepatocellular carcinoma was 38.5 cancers per 100 000 person-years for all chronic HBV-infected persons, with rates for persons less than 50 years of age of 17.5 cancers per 100 000 person-years, and for those aged 50 years and older of 113.3 cancers per 100 000 person-years. Rates of lung cancer and female genital cancer were also statistically significantly higher among the chronically HBV-infected compared with HBV-negative persons. No statistically significant differences in cancer incidence were observed between HBV-immune and HBV-negative persons.

**Figure 1.** Age-specific morbidity rates per 100 000 person-years for chronic liver disease (chronic nonalcoholic liver diseases and chronic hepatitis; see Table 2 legend) on log scale by hepatitis B virus (HBV) status and sex.

**Table 3.** Incidence rate ratios (IRRs) for cancer by hepatitis B Virus (HBV) status in a population-based cohort of 8879 persons in Greenland*  

<table>
<thead>
<tr>
<th>Cancer site†</th>
<th>All</th>
<th>Chronically HBV infected (HBsAg‡)</th>
<th>HBV immune‡ (HBsAg— and HBcAb+)</th>
<th>HBV negative (HBcAb–)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case patients</td>
<td>Case patients</td>
<td>Adjusted IRR (95% CI)§</td>
<td>Case patients</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>15</td>
<td>5</td>
<td>8.70 (2.06 to 36.7)</td>
<td>7</td>
</tr>
<tr>
<td>Men</td>
<td>13</td>
<td>5</td>
<td>8.47 (2.00 to 35.8)</td>
<td>5</td>
</tr>
<tr>
<td>Women</td>
<td>2</td>
<td>0</td>
<td>NE</td>
<td>2</td>
</tr>
<tr>
<td>Intestinal</td>
<td>176</td>
<td>14</td>
<td>1.32 (0.74 to 2.36)</td>
<td>92</td>
</tr>
<tr>
<td>Nasopharyngeal</td>
<td>48</td>
<td>5</td>
<td>1.25 (0.47 to 3.29)</td>
<td>15</td>
</tr>
<tr>
<td>Respiratory organs</td>
<td>137</td>
<td>16</td>
<td>2.27 (1.28 to 4.04)</td>
<td>67</td>
</tr>
<tr>
<td>Bone, tissue, muscles</td>
<td>9</td>
<td>1</td>
<td>1.90 (0.29 to 17.8)</td>
<td>2</td>
</tr>
<tr>
<td>Skin</td>
<td>20</td>
<td>2</td>
<td>1.34 (0.29 to 6.15)</td>
<td>1</td>
</tr>
<tr>
<td>Breast</td>
<td>87</td>
<td>6</td>
<td>0.67 (0.20 to 2.20)</td>
<td>37</td>
</tr>
<tr>
<td>Female genitals</td>
<td>86</td>
<td>11</td>
<td>1.87 (0.89 to 3.92)</td>
<td>37</td>
</tr>
<tr>
<td>Male genitals</td>
<td>18</td>
<td>2</td>
<td>2.64 (0.52 to 13.4)</td>
<td>5</td>
</tr>
<tr>
<td>Bladder</td>
<td>29</td>
<td>1</td>
<td>0.56 (0.07 to 4.38)</td>
<td>12</td>
</tr>
<tr>
<td>CNS and eye</td>
<td>22</td>
<td>0</td>
<td>NE</td>
<td>12</td>
</tr>
<tr>
<td>Endocrine</td>
<td>8</td>
<td>2</td>
<td>3.87 (0.68 to 21.9)</td>
<td>2</td>
</tr>
<tr>
<td>Blood</td>
<td>27</td>
<td>1</td>
<td>0.34 (0.05 to 2.59)</td>
<td>10</td>
</tr>
<tr>
<td>Cancer, non-localized</td>
<td>22</td>
<td>5</td>
<td>3.83 (1.23 to 12.0)</td>
<td>9</td>
</tr>
<tr>
<td>Metastases</td>
<td>116</td>
<td>8</td>
<td>1.15 (0.54 to 2.44)</td>
<td>51</td>
</tr>
</tbody>
</table>

* HBcAb = Hepatitis B core antibody; HBsAg = Hepatitis B surface antigen; NE = not estimated; = negative, + = positive.
† Diagnoses were based on International Classification of Diseases (ICD-8; 1987–1993) and ICD-10 (1994 to present) codes. The categorizations were based on the guidelines from the Danish Cancer Registry, as follows: Hepatocellular carcinoma: 15509, 15589 DC220, DC227, DC229; Intestinal cancers: 150-54, 15519, 156-159, 19509, 19519, DC15-DC21, DC221-4, DC23-DC26, DC762-DC783; Nasopharyngeal cancers: 140-149, 19580, 19591, DC00-DC14, DC760; Respiratory organs: 160-163, DC30-DC34, DC39, Bone, tissue, muscle cancers: 170, 171, 19583, DC40-DC41, DC45-DC49, DC764-DC765; Skin cancers: 172-173, DC43-DC44; Breast cancers: 185-187, DC60-DC63; Bladder cancers: 188-189, DC64-DC68; CNS and Eye cancers: 190-192, DC89-DC72; Endocrine cancers: 193, 194, DC73-DC75; Blood malignancies: 200-207, DD45, DD46, DD471, DD473, DC81-DC96; Cancer, non-localized: 195, DC80; Metastases: 196-198, DC77-DC79.
‡ The immune group included 477 persons who were HBcAb positive, but HBsAg could not be estimated due to insufficient serum or an inconclusive HBsAg test result.
§ For each individual, person-years were calculated from the time of the first HBV test result in any database or January 1, 1987, whichever came later, until the date of diagnosis, death, emigration or December 31, 2008, whichever came first. The model was adjusted for age (splines), sex, period (splines), and ethnicity.

**All-Cause Mortality**  
In total, 1304 (14.7%) of the 8879 persons had died at the end of follow-up (March 31, 2010). Of chronically HBV-infected persons, 124 (19.1%) had died; of HBV-immune persons, 606 (19.7%) had died; and of HBV-negative persons, 574 (11.1%) had died. All-cause mortality rate was 1.55 (95% CI = 1.23 to 1.94) times higher for Inuit compared with non-Inuit or mixed race participants. For chronically HBV-infected persons, all-cause mortality was 1.47 (95% CI = 1.21 to 1.79) times higher than for HBV-negative persons. This increase was seen in both men and women (in men, IRR = 1.23, 95% CI = 0.95 to 1.61; in women, IRR = 1.90, 95% CI = 1.41 to 2.55; $p_{sex} = .03$), and in persons...
older and younger than 50 years of age (for persons aged <50, IRR = 1.25, 95% CI = 0.90 to 1.75; for persons aged ≥50, IRR = 1.62, 95% CI = 1.27 to 2.06; $P_{age<50 \text{ vs } \geq 50} = .22$), and for persons born before and after January 1, 1945 (for persons born before January 1, 1945, IRR = 1.70, 95% CI = 1.31 to 2.21; for persons born in 1945 or after, IRR = 1.26 [95% CI = 0.94 to 1.70]; $P_{born before vs after January 1, 1945} = .14$).

The sex- and age-specific overall mortality rates per 100 000 person-years for chronically HBV-infected persons were generally higher than those for HBV-negative persons; this increase was the same regardless of sex or age (Figure 2). All-cause mortality rate in HBV-immune persons was 1.17 (95% CI = 1.04 to 1.32) times higher than that in HBV-negative persons.

**Discussion**

In this large population-based cohort study, we report morbidity and mortality in Greenland by HBV status for the first time to our knowledge. Chronic HBV infection was associated with markedly increased rates of liver diseases that are known to be associated with HBV infection as well as all-cause mortality compared with rates in HBV-negative persons. However, the incidence of hepatocellular carcinoma and cirrhosis among chronically HBV-infected persons was low compared with population-based estimates from countries with low, intermediate, and high rates of endemic HBV infection.

The statistically significant increase in overall liver morbidity in chronic HBV-infected persons, compared with HBV-negative persons, could be attributable to increased risks of nonalcoholic cirrhosis, chronic hepatitis, and acute hepatitis. However, compared with other countries with high HBV incidences, we still found very low rates of hospitalization due to hepatic conditions in Greenland. Among Alaskan natives, McMahon et al. (22) found incidence of chronic hepatitis that was twofold higher and of cirrhosis that was fourfold higher than those we saw in Greenland. In Taiwan, the age-adjusted incidence of cirrhosis among asymptomatic chronic HBV carriers with undetectable HBV DNA (23) was more than 10 times higher (339 cases per 100 000 person-years) than in our population of chronic HBV carriers. Similarly, the incidence of hepatocellular carcinoma among chronically HBV-infected persons in Greenland was lower than the incidence of hepatocellular carcinoma among chronically HBV-infected persons reported for multiple countries in which there are low, intermediate, or high rates of endemic HBV infection (24–33). For example, although we report a rate of 38.5 hepatocellular cancers per 100 000 person-years among chronic HBV-infected persons in Greenland, the corresponding rates in the literature are 65 hepatocellular cancers per 100 000 person-years in Sweden (25), 67 cancers per 100 000 person-years in Australia (24), 196 cancers per 100 000 person-years among Alaskan natives (28), and 216 cancers per 100 000 person-years in Korea (32). Furthermore, the observed rate ratio for hepatocellular carcinoma in chronically HBV-infected persons in Greenland compared with HBV-negative persons was lower than or of the same magnitude as the relative risks observed in other countries with a high prevalence of HBV carriers (28–32) and lower than the relative risks in countries such as Australia (24) and Sweden (25) that have a low prevalence of HBV carriers. The lower-than-expected world standardized rates of liver morbidity in chronically HBV-infected persons in Greenland and the low rate ratio when comparing chronic HBV-infected with HBV-negative persons suggest that the overall low incidence of HBV-related morbidity in Greenland is most likely due to a lower than usual incidence of hepatocellular cancer in chronically HBV-infected persons and that HBV infection may exhibit a more benign course in Greenland than in other parts of the world.

A number of factors could explain why the course of HBV infection might be more benign in Greenlanders. In contrast to high-endemic countries in Asia and in Alaska (1,34–36), HBV infection in Greenland appears to be transmitted mainly during adolescence and adulthood (6–8,13,37). Children infected perinatally are at higher risk of cirrhosis and hepatocellular carcinoma than those infected in adolescence and adulthood (29,38,39). However, in Australia (24), Sweden (25), and Spain (26), low-endemic countries where HBV transmission mainly occurs in adulthood, the incidence of hepatocellular carcinoma and liver diseases among chronic carriers is still approximately two times higher than the incidence among chronic carriers in our cohort.

In Greenland, HBV genotypes D and B6 are the predominant subtypes (6,40–42). HBV genotype has been shown to be strongly associated with severity of sequelae (43). Genotype D is the most widespread HBV genotype worldwide (44) and is associated with cirrhosis and hepatocellular carcinoma in older individuals (45). Genotype B6 is found among indigenous population in the circumpolar area, whereas the Bj (B1) genotype is primarily found in Japan (41). Genotypes B1 and B6 are both “pure” HBV genotypes, whereas the Ba, or B Asia (B2–5), genotypes include a recombinant portion from the genotype C core region. Genotype Ba has been associated with a higher incidence of hepatocellular carcinoma than genotype B1; in addition, genotype Ba–associated hepatocellular carcinoma occurs a decade earlier, on average, than hepatocellular carcinoma associated with genotype B1 (41). Among the Inuit in Alaska, genotypes F and C are both associated with a higher incidence of hepatocellular carcinoma than genotypes D, B6, and A2. In the high-endemic countries in Asia, genotypes C and Ba predominate; both genotypes are associated with a high risk of hepatocellular carcinoma (45–49). With these differences in mind, the observed lower burden of disease in Greenland could in theory be explained by differences in genotype distribution.

The absence of other risk factors may also contribute to the lower than expected hepatocellular carcinoma incidence observed in this population. For example, aflatoxin, a carcinogenic substance found in contaminated grains and groundnuts, has been identified as a strong cofactor for hepatocellular carcinoma in Asia and

**Figure 2.** Age-specific mortality rates per 100 000 person-years on log scale by hepatitis B virus (HBV) status and sex.
Africa, whereas it is unlikely to be found in Greenland. Lower rates of hepatocellular carcinoma could be ascribed to low alcohol or tobacco consumption. We did not have such data on an individual level for our cohort. However, in 1999, more than 70% of the Greenlandic population smoked (50), and the incidence of lung cancer in men and women was among the highest in the world (11). Furthermore, the alcohol consumption per capita is high in Greenland (12.3 L/y), above the average consumption in Europe and markedly higher than in the United States (8.6 L/y in 2003) (51). By contrast, the prevalence of hepatitis C infection, a known risk factor for hepatocellular cancer, is less than 1% in Greenland (6,52) and could contribute to the lower rate of cancer in Greenland as compared with elsewhere.

The low incidence of hepatocellular carcinoma and other HBV-related conditions in HBV-infected persons in Greenland could also suggest that the immunologic response to HBV in Greenlanders differs from that in other populations. For example, impaired targeting of infected hepatocytes would minimize immune-mediated cell death and HBV-related morbidity. Twin studies and family studies have demonstrated a potential genetic influence on the response to HBV infection (53,54). Other studies have examined the influence of various host genetic factors (55–62), HLA class I and II (63), cytokines (eg, tumor necrosis factor-α and interleukin-10) (53), mannose-binding lectin (64,65), and vitamin D receptor (66–69) on susceptibility to HBV infection and risk of chronic infection, cirrhosis, and hepatocellular carcinoma, with conflicting results. No studies of the impact of various genetic polymorphisms on the risk of sequelae following HBV infection have been conducted in Greenland, and no studies have addressed genetic differences between HBV-infected individuals in Greenland and Alaska. The Inuit population in Greenland is supposed to have originated from the Neo-Eskimo Thule culture people who migrated from Alaska across Canada 1000 years ago (70–72). Although a close genetic relationship can be expected between Inuit across the Arctic, there is little knowledge about specific genetic similarities and dissimilarities between the Inuit of different areas and between Inuit and other Eskimo groups in Alaska (Yupik and Aleutians).

The relatively young age of the individuals in our cohort may also help to explain the lower incidence of hepatocellular carcinoma in Greenland, compared with elsewhere. Because the mean age at recruitment of HBsAg-positive individuals in this study was 33.4 years (Table 1) and the median follow-up period was 22.8 years, cohort members were on average in their mid-50s when hepatocellular carcinoma incidence was estimated. Hepatocellular carcinoma associated with HBV infection tends to occur later in life, however. Thus, the incidence of hepatocellular carcinoma may increase in our cohort as it continues to age.

Even though the incidence of hepatocellular carcinoma among chronically HBV-infected persons in Greenland appears lower than in other groups of chronically infected persons, the 8.7-fold increased risk of hepatocellular carcinoma as well as the hepatocellular carcinoma diagnosed at a younger age than among the HBV-negative individuals underscore the importance of following up chronic HBV-infected persons in Greenland.

We found that chronic HBV carriers had statistically significantly higher risks of lung cancer, cervical cancer, and tuberculosis compared with HBV-negative persons. Because HBV is not a known cause of these diseases, the higher risks among HBV-infected persons are most likely explained by confounding factors. Smoking and human papillomavirus (HPV) infection are risk factors for lung (73) and cervical cancer (74,75), respectively. Low socioeconomic status (76) and number of sexual partners (74) are associated with tuberculosis, and smoking and number of sexual partners are associated with HPV infection. It is conceivable that HBV is more prevalent in lower social classes and that chronic carriers have more sexual partners and a greater incidence of HPV. Thus, the apparent association of HBV infection with non–liver-related morbidity most likely is due to confounding by socioeconomic status, cigarette smoking, and sexual behavior.

The all-cause mortality rate for HBV chronic carriers was 47% higher than the rate among HBV-negative persons. As shown in Figure 2, this increase was the same regardless of sex or age. Similar increases in all-cause mortality were observed Taiwan (77) and Australia (78), where chronic carriers had 70% and 40% higher mortality, respectively, than the general population. By contrast, all-cause mortality in HBsAg-positive persons in Sweden and the Haimen province of China has been shown to be 130% and 260% higher, respectively, than in the general population (4,79). Although it is difficult to compare these findings directly due to differences in study groups, all studies find higher all-cause mortality rates in chronically HBV-infected persons compared with HBV-negative persons. Whereas some of the increase may be explained by HBV-related morbidity, higher rates of other diseases, such as non-hepatocellular carcinoma cancers, in chronic carriers, as well as lifestyle-related factors such as excess cigarette use are likely to play a role.

Strengths of this study include the population-based cohort design with selection and follow-up of participants irrespective of HBV status. Accurate and timely information on the vital status of all participants was obtained from the CRS system, which is validated and updated on a daily basis. This minimized bias due to selection of participants and loss to follow-up.

Some persons who were classified as HBV-negative might not have been recognized as having converted to chronic HBV carriers because they were not subsequently tested. However, any bias caused by misclassification is most likely small and does not affect the estimated world standardized rates of morbidity in chronic carriers. Furthermore, as HBV testing was independent of subsequent morbidity and mortality, any misclassification would only lead to bias of the estimated rate ratios toward unity.

We used only our own HBV test results and test results from the laboratory in Nuuk (the only microbiological laboratory in Greenland) to determine HBV status. Both laboratories used MEIA kits from the same manufacturer, which ensured a high degree of laboratory validity.

We required only a single positive HBsAg test to designate a person a chronic HBV carrier. However, the majority of persons had more than one positive HBsAg test during follow-up. We acknowledge that persons with a positive result could include some newly HBV-infected persons who would later overcome the infection and become immune. However, in an acute self-limited infection, HBsAg will only be present for 2–3 months (80,81). Thus, we consider it likely that any inclusion of persons who later became
immune had a negligible impact in our population-based survey of apparently healthy persons and any bias would be such that the true association is stronger than the one observed.

Liver disease diagnoses may have been underreported because patients with subclinical cancers may not have been hospitalized. Also, we also cannot rule out the possibility of missed cancers due to diagnostic misclassification. However, we used the National Discharge Registers to identify cirrhosis patients based on both biopsy and/or clinical manifestations, in contrast to diagnoses in other studies that were only based on biopsy findings (23,82). Thus, our case finding is more complete and includes less severe cases. Furthermore, our department is currently validating the Greenlandic Discharge register thoroughly. In the first internal rapport to the Greenlandic Health Rule, we have described the register as valid and usable for research and evaluation. We cannot rule out overall lower rates of hospitalization in Greenland as compared with other countries. However, 15 of the 16 towns have hospitals, and many of the settlements have health clinics. In addition, health care in Greenland is free of charge, making it little likely that socioeconomic as well as locational differences dictate access to care and hospitalization.

The validity and completeness of the Danish Cancer Registry (which includes Greenland) have previously been evaluated. The information in the register has been shown to be of high quality, and the fact that multiple sources notify the register of tumors results in a high degree of completeness and accuracy (19,20). However, the reporting of cancers from Greenland has not specifically been evaluated, but reporting of cancer patients using equivalent procedures is mandatory in Denmark and Greenland. Judged by the fraction of unknown cancers in our study (2.7%) and for the Greenlandic population (4.0%) (11), cancer registration in Greenland seems to be of the same quality as in many European countries, including Denmark (4.0%–4.3%) (83). Furthermore, in a Greenlandic study on the influence of migration on cancer patterns, the largest increase in cancer risk after emigration was observed for cancers detectable without advanced equipment (mouth, breast, skin, bladder, and testis) (84). However, to reduce the risk of non- or misclassification, we included hepatocellular carcinoma patients from both the Danish and Greenlandic Hospital Discharge Registries and the Cancer Registry (17,19,20).

In this large population-based study among Greenlanders, we found chronic HBV-infected persons to have an increased risk of liver disease compared with HBV-negative persons. However, the standardized incidence rates for hepatocellular carcinoma and cirrhosis for chronic carriers in Greenland were lower than the rates in chronic carriers in other populations. This finding could in theory be explained by the circulation of less pathogenic HBV genotypes among Greenlanders and/or by the absence of previously identified cofactors for hepatocellular carcinoma. The Greenlandic immune response to HBV infection also needs to be explored to determine if differences (compared with other populations) might result in less morbidity than seen in other endemic populations.

References


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