Greenland remains a highly endemic area for hepatitis B virus (HBV) infection. This is in sharp contrast to other modern societies, such as Denmark. To address this discrepancy, we investigated the natural history of HBV infection in Greenland by estimating the age-specific incidence of HBV infection, the proportion of chronic carriers, and the rates of hepatitis B surface antigen seroclearance. In total, 8,879 Greenlanders (16% of the population) from population-based surveys conducted in 1987 and 1998 were followed through March 2010. Data on HBV status were supplemented by HBV test results from all available HBV registries in Greenland to determine changes in HBV status over time. Incidence rates of HBV infection and hepatitis B surface antigen seroclearance were estimated after taking into account interval censoring. The incidence of HBV infection in 5–14-year-old subjects was less than 1 per 100 person-years and peaked at 5 per 100 person-years in persons 15–24 years of age. Overall, 17.5% of persons infected in adulthood were estimated to become chronic carriers. HBV is primarily transmitted in adolescence and adulthood in Greenland. In contrast to what is observed in most other populations, HBV-infected adults in Greenland have a high risk of progressing to chronic HBV carriage. This phenomenon might explain how the high rate of infection is maintained in Greenland.

Arctic; cohort study; Greenland; hepatitis B; incidence; population-based study

Abbreviations: CRS, Central Registration System; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

Worldwide, infection with the hepatitis B virus (HBV) is a major health problem. In highly endemic countries in Asia, vertical transmission is the predominant mode of infection, whereas in the highly endemic countries in sub-Saharan Africa, most infections are believed to occur horizontally among children (1–4). In lowly endemic countries, the predominant modes of transmission in adulthood are unprotected intercourse, intravenous drug use, and exposure to blood products (5).

The risk of chronic infection depends on age at infection. Vertically infected children born to chronic carriers who have a high viral load have up to a 90% risk of becoming carriers (4, 6, 7). Of those infected when they are younger than 5 years of age, 25%–30% become chronic carriers; however, fewer than 10% of infections in immunocompetent adults result in chronic carriage (8). In chronic carriers of HBV, seroclearance of hepatitis B surface antigen (HBsAg) increases with age (9, 10).

Earlier studies have shown that HBV is endemic in Greenland, with 40%–45% of the population being positive for hepatitis B core antibody (HBcAb) and 5%–10% being positive for HBsAg (11–13). However, previous studies were cross-sectional, that is, they described the age-specific prevalence of HBV infection markers. Despite the high rate of chronic carriers of HBV, clinical hepatitis, cirrhosis, and hepatocellular carcinoma have been reported less frequently than expected in the same population (14–17). In the present prospective population-based cohort study of 8,879 Greenlanders (≈16% of the population) with a follow-up time of
up to 23 years, we determined age-specific HBV prevalence, incidence, and proportion of chronic carriers, as well as spontaneous HBsAg seroclearance rates among chronic carriers.

METHODS

Greenland is an island with 16 towns and approximately 60 settlements, all of which are located along the coast line. Of the 56,000 inhabitants, 85% are Inuit and 15% are not (mostly Danes). The Civil Registration System (CRS) includes all persons who have lived in Greenland at some point since January 1, 1972 (18). Each person is assigned a unique personal CRS identification number that is used for all administrative purposes and can be used to link information from national registers. The CRS is continuously updated and contains information on date and place of birth, sex, address, parents, and date of death or emigration. In the present study, we defined being of Inuit ethnicity as having 2 parents born in Greenland; if the father was not identified, ethnicity was determined based on the maternal birthplace only (19).

Study cohort

The study cohort consisted of persons who participated in a minimum of 1 of 2 serosurveys in 1987 and 1998. The 1987 survey was a population-based screening survey for syphilis reactivity in 2 districts in West Greenland (Aasiaat and Maniitsoq) and 4 districts in South Greenland (Nanortalik, Qaqortoq, Narsaq, and Paamiut). Of 14,006 randomly selected persons aged 15–70 years, 7,609 participated (54%) (20), and sera from 6,170 persons remained available. The participation rate was higher in the southern districts (64%) than in the western districts (43%), was higher among women (60%) than among men (49%), and decreased with increasing age (20). The 1998 survey was a population-based screening for human immunodeficiency virus in the Sisimiut District in West Greenland (21). That study population consisted of all persons in the district who were older than 5 years of age. Of 4,807 possible participants, 2,858 (59%) participated (66% of females and 53% of males), with participation rates being higher among children aged 5–17 years (86%) than among adults (50%) (21). Sera from 2,709 remained available.

After identifying current addresses in the CRS, we sent a letter with information about the study to all persons from the 1987 serosurvey who were alive on March 1, 2007. The letters provided participants with the opportunity to decline having their stored serum tested for HBV. Participants from the 1998 survey had already given written consent for future analyses of their stored serum.

The stored serum samples were tested for HBV markers in the Department of Virology at Statens Serum Institut, Copenhagen, Denmark, using microparticle enzyme immunoassay kits (Abbott GmbH & Co. KG, Wiesbaden, Germany). All samples were first tested for HBcAb; positive samples were also tested for HBsAg. To learn about changes in the participants’ HBV statuses over time, additional HBV results from all available HBV registries in Greenland were used. The HBV Incidence Notification Register (1987–1991) included all new cases of HBV infection that were voluntarily reported by the hospitals to the Chief Medical Officer. The Greenlandic Hepatitis B Database, which has operated from 1992 to the present, records HBV test results in Greenland, which all are performed at Queen Ingrid’s Hospital in Nuuk (the capital) using radioimmunoassay kits (Abbott GmbH & Co. KG). Finally, a follow-up study was conducted in which the HBsAg-negative carriers from the 1987 and 1998 surveys who were alive on November 1, 2007, were frequency-matched 1:1.5 by age, sex, and district of residence with immune and HBV-negative persons randomly drawn from the original cohorts. Cases and controls were invited to participate. Participants were bled between March 2008 and December 2009. The blood was centrifuged, serum and plasma were separated from buffy coat, and the material was immediately frozen at −20°C. Within 3 weeks, it was shipped at −20°C to Denmark and kept at −80°C until it was tested for HBV markers at the Department of Virology at Statens Serum Institut, Copenhagen, Denmark.

Assessment of HBV status

On the basis of HBcAb and HBsAg test results, HBV infection status was defined as chronic (positive for HBcAb and HBsAg), immune (positive for HBcAb and negative for HBsAg), or HBV-negative (negative for HBcAb). If the sample was HBcAb-positive but HBsAg positivity or negativity could not be determined, the HBV status was based on results from the other databases; otherwise, these HBcAb-positive persons were characterized as immune as to avoid overestimation of the number of HBV chronic carriers. Because the HBV database only contained HBsAg test results, an HBV-negative person who later tested HBsAg-negative in the HBV database was defined as not chronic (i.e., either HBV-negative or immune). The study complied with the Helsinki Declaration II and was approved by the Commission for Scientific Research in Greenland and the Danish Data Protection Agency.

Statistical analyses

The study data consisted of longitudinal HBV test results and can thus be viewed as interval-censored data; that is, the data contain information on whether HBV status changed between 2 tests (or between birth and the first test) but not precisely when HBV status changed. Therefore, we took interval censoring into account when estimating the age-specific incidence of HBV infection by using a Turnbull estimator, as described further in the Appendix.

The proportion of chronic carriers among the HBV-infected participants was estimated in 2 ways. First, we determined the proportion of chronic carriers among the HBV-infected participants at the time of the first test (in either 1987 or 1998). Proportions were compared by age group (5–14, 15–19, 20–29, 30–44, or ≥45 years) and sex using logistic regression analysis (PROC GENMOD in SAS, version 9.2; SAS Institute Inc., Cary, North Carolina). In the second approach, the proportion was estimated as the ratio of the proportion of chronic carriers among HBV-infected persons using the age-specific incidence of HBV infection that would subsequently lead to chronic carriage and the overall age-specific incidence of HBV infection. We evaluated the proportion according to estimated age at infection rather than age at testing. The latter
Table 1. Demographic Characteristics by Hepatitis B Status at First Test Result in 1987 or 1998 in Population-Based Cohort Study \((n = 8,879)\), Greenland

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All(^a)</th>
<th>Chronic Carriers(^b) (HBsAg-Negative and HBcAb-Positive)</th>
<th>Immune(^c) (HBcAb-Positive)</th>
<th>Total No. Infected With HBV (HBcAb-Positive)</th>
<th>Crude (P) Value(^d)</th>
<th>Adjusted (P) Value(^e)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number tested</td>
<td>8,879</td>
<td>650 (7.3)</td>
<td>3,069 (34.6)</td>
<td>3,719 (41.9)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1987</td>
<td>6,170</td>
<td>478 (7.8)</td>
<td>2,319 (37.6)</td>
<td>2,797 (45.4)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1998</td>
<td>2,709</td>
<td>172 (6.4)</td>
<td>750 (27.7)</td>
<td>922 (34.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at testing, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5–9</td>
<td>435</td>
<td>4 (0.9)</td>
<td>9 (2.1)</td>
<td>13 (3.0)</td>
<td>0.0002</td>
<td>0.0002</td>
</tr>
<tr>
<td>10–14</td>
<td>531</td>
<td>6 (1.1)</td>
<td>32 (6.0)</td>
<td>38 (7.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15–19</td>
<td>1,195</td>
<td>55 (4.6)</td>
<td>234 (19.6)</td>
<td>289 (24.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–29</td>
<td>2,591</td>
<td>222 (8.6)</td>
<td>899 (34.7)</td>
<td>1,121 (43.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30–39</td>
<td>1,811</td>
<td>177 (9.8)</td>
<td>786 (43.4)</td>
<td>963 (53.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–49</td>
<td>1,254</td>
<td>109 (8.7)</td>
<td>595 (47.5)</td>
<td>704 (56.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–64</td>
<td>935</td>
<td>67 (7.2)</td>
<td>436 (46.6)</td>
<td>503 (53.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥65</td>
<td>127</td>
<td>10 (7.9)</td>
<td>75 (59.1)</td>
<td>85 (66.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age,(^f) years</td>
<td>30.5 (14.4)</td>
<td>33.4 (12.4)</td>
<td>35.6 (13.4)</td>
<td>35.2 (13.3)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age in 1987,(^f) years</td>
<td>31.2 (12.1)</td>
<td>32.2 (11.3)</td>
<td>33.6 (12.1)</td>
<td>33.4 (11.9)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age in 1998,(^f) years</td>
<td>28.8 (18.4)</td>
<td>36.7 (14.5)</td>
<td>41.7 (15.5)</td>
<td>40.8 (15.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4,390</td>
<td>359 (8.2)</td>
<td>1,440 (32.8)</td>
<td>1,799 (41.0)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>4,489</td>
<td>291 (6.5)</td>
<td>1,629 (36.3)</td>
<td>1,920 (42.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity(^g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Inuit</td>
<td>7,874</td>
<td>625 (7.9)</td>
<td>2,944 (37.4)</td>
<td>3,569 (45.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>346</td>
<td>12 (3.5)</td>
<td>47 (13.6)</td>
<td>59 (17.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Inuit</td>
<td>620</td>
<td>8 (1.3)</td>
<td>66 (10.7)</td>
<td>74 (11.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>39</td>
<td>5 (12.8)</td>
<td>12 (30.8)</td>
<td>17 (43.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital at testing (listed from north to south)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Aasiaat</td>
<td>1,510</td>
<td>183 (12.1)</td>
<td>617 (40.9)</td>
<td>800 (53.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sisimiut</td>
<td>2,709</td>
<td>172 (6.4)</td>
<td>750 (27.7)</td>
<td>922 (34.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maniitsoq</td>
<td>718</td>
<td>49 (6.8)</td>
<td>351 (48.9)</td>
<td>400 (55.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paamiut</td>
<td>1,069</td>
<td>61 (5.7)</td>
<td>347 (32.5)</td>
<td>408 (38.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Narsaq</td>
<td>747</td>
<td>21 (2.8)</td>
<td>217 (29.1)</td>
<td>238 (31.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Qaqortoq</td>
<td>1,391</td>
<td>76 (5.5)</td>
<td>441 (31.7)</td>
<td>517 (37.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nanortalik</td>
<td>735</td>
<td>88 (12.0)</td>
<td>346 (47.1)</td>
<td>434 (59.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen.

\(^a\) The participants were entered into the study at the time of their first hepatitis B virus test result that was in any included database. Thus, baseline characteristics for participants who appeared in both cohorts \((n = 84)\) are based on data from the 1987 testing.

\(^b\) Positive for HBsAg.

\(^c\) The immune group included 393 persons who were HBcAb-positive but for whom HBsAg status could not be determined because of sparse serum (177 samples were only tested for HBcAb) or because the confirmatory HBsAg test result (done on samples with HBsAg S/N values between 2 and 3) was either inconclusive \((n = 179)\) or could not be performed because of sparse material \((n = 37)\).

\(^d\) Proportions of chronic carriers, immune subjects, and hepatitis B virus–negative persons at the first test result in 1987 or 1988 by selected variables were compared using polytom logistic regression models estimated by SAS PROC NLMIXED (SAS Institute, Inc., Cary, North Carolina). Mean ages were compared using linear regression.

\(^e\) The model was adjusted for age (grouped as in Table 1), sex, ethnicity, and hospital at which primary testing was done.

\(^f\) Values are presented as mean (standard deviation).

\(^g\) We defined Inuit ethnicity as having 2 parents born in Greenland; if the father was not identified, ethnicity was based on the maternal birthplace only.
approach is further described in the Appendix. The HBsAg seroclearance rate was estimated using a Turnbull estimator, similar how HBV incidence was estimated (Appendix).

All analyses were performed using SAS. A 2-sided \( P \) value of <0.05 was considered significant.

RESULTS

Of 8,983 potential participants from the 1987 (6,267 persons) and 1998 (2,716 persons) surveys, 104 persons (1.2%) were excluded either at their request (46 persons) or because of an invalid CRS number (58 persons). At the date of enrollment, 41.9% had evidence of HBV infection and 7.3% were HBsAg-positive (Table 1). The prevalence of HBV markers increased from 3% among 5–9-year-old children to 53.8% among 30–39-year-old adults, whereas the prevalence of HBsAg carriage increased from 0.9% among 5–9-year-old children to 9.8% among 30–39-year-old adults. Because the participation rates differed by sex and district of residence in the original surveys (1987 and 1998), we calculated the HBV prevalence in the total cohort as an estimate weighted by participation rates. However, these weighted estimates (7.8% chronic carriers and 42.8% HBV-infected persons) did not differ from the estimates based on the participants only.

HBV infection incidence

On the basis of these prevalence data and an additional 6,059 HBV results from all available databases and the follow-up study (Figure 1), we estimated the age-specific incidence of HBV infection per 100 person-years. Figure 2A–2C depicts estimated incidence overall and in male and female subjects, respectively. The incidence among 5–14-year-old children was based on data from the 1998 cohort only because children were not included in the 1987 survey and the incidence was less than 1 per 100 person-years during childhood. The incidence of HBV infection was highest (5 per 100 person-years) among 15–24-year-old participants. Thereafter, it fell rapidly to 1 or fewer per 100 person-years in participants who were 45 years of age or older (Figure 2A). For male participants, the HBV infection incidence fell rapidly after 24 years of age, whereas the decrease with age was less abrupt for female participants (Figure 2B and 2C). The average incidence of HBV infection among the 15–44-year-old participants was 2.0 (95% confidence interval, 1.9, 2.1) per 100 person-years.

Proportion of chronically infected

Overall, 17.5% (95% CI: 16.3, 18.7) of those with evidence of HBV infection were HBsAg carriers. This proportion varied by age (\( P = 0.0002 \)) (Table 1). The difference was due to the difference between participants who were 5–44 years of age and those who were 45 years of age or older (\( P < 0.001 \)); there were no differences between the subgroups within the 5–44 years age range (\( P = 0.86 \)). The proportion also varied by sex (\( P < 0.0001 \)). Among 15–44-year-old participants, the proportion of chronic carriers was 16.4% (95% CI: 14.5, 18.4) among female subjects and 21.7% (95% CI: 19.5, 23.9) among male subjects. We also estimated the proportion of chronic carriers among HBV-infected persons using the age-specific incidence of HBV infection that would subsequently lead to chronic carriage. We evaluated the proportion according to estimated age at infection rather than age at testing. In that analysis, the proportion of HBV-infected 15–44-year-old subjects who became chronic carriers was 22.7% (95% CI: 20.2, 25.2).

HBsAg seroclearance

Figure 3 depicts the spontaneous HBsAg seroclearance rate among chronic carriers. Among 406 chronic carriers, 121 (29.8%) had HBsAg clearance during a mean follow-up of 19.8 years. The estimated annual seroclearance rate was
0.83 per 100 person-years (95% CI: 0.57, 1.09), and it varied significantly with age ($P < 0.0001$) (Figure 3). It peaked in the age group of 50–59 years at 2.0 per 100 person-years; for persons younger than 50 years of age, the rate was 0.70 per 100 person-years, and for persons 50 years of age or older, the rate was 1.5 per 100 person-years. The median age of seroclearance was 44 years (interquartile range, 34–53), and the mean age was 44.5 (standard deviation, 12.5) years. By 75 years of age, the cumulative probability of having experienced HBsAg seroclearance was 50%. Among persons 50 years of age or older, we found no difference in seroclearance rates between the sexes (for women vs. men, $P = 0.81$); however among persons younger 50 years of age, women had a significantly rate of clearance than did men (for women vs. men, $P = 0.0008$).

**DISCUSSION**

In the present population-based cohort study with a follow-up time of up to 23 years, we have for the first time estimated the age-specific incidences of HBV infection and HBsAg seroclearance, as well as the proportion of chronic HBV carriers, in Greenland. The age-specific incidence pattern indicated that HBV infection in Greenland is mainly transmitted in adolescence and adulthood. The high proportion of infected adults who developed chronic infection is intriguing and might contribute to the high HBV prevalence in Greenland. Among chronic carriers, the incidence of HBsAg seroclearance appeared to be similar to those found in other longitudinal studies.

**HBV prevalence and incidence**

The incidence of HBV infection among 15–24-year-old participants (5 per 100 person-years) was markedly higher than the incidence among 5–14-year-old participants. Furthermore, the HBcAb prevalence among persons aged 20–29 years was 6-fold higher than that in persons aged 10–14 years, which indicates a high transmission rate during adolescence. This increase could potentially be attributable to different infection rates in different birth cohorts. However, using data on blood samples collected in 1965–1970, Skinhoj et al. (11) studied 2,904 Inuit from most districts in Greenland (15–70 years of age) and found an overall HBsAg-positivity
rate of 7.1%, with the highest frequency among 20–30-year-old subjects (10%). In 1981, Melbye et al. (15) examined 178 Inuit persons who were 0–20 years of age and found that none of the 78 subjects who were 0–9 years of age were HBsAg-positive, whereas among 10–20-year-old subjects, 21% were hepatitis B surface antibody–positive and 10% were HBcAb-positive. In 1994, Langer et al. (13) studied 507 Inuit (age range, 7–79 years) in 2 west coast towns (Sisimiut and Ilulissat). In total, 11% of the 10–19-year-old Inuit were HBCAb-positive, whereas 57% of 30–39-year-old Inuit were HBCAb-positive. The overall HBsAg prevalence was 7%, with the highest prevalence (14%) among 30–39-year-old subjects and the lowest (only 2%) among 10–19-year-old subjects. All cross-sectional studies from 1965 to 1994 indicated low HBV transmission among children. The results of the studies suggest that HBV transmission in Greenland mainly occurs among adolescents and young adults, regardless of birth year.

Most studies on HBV incidence were not population-based but rather were studies of subpopulations. The incidence among 15–24-year-old subjects in our study (5 per 100 person-years) was higher than the incidence (1.5 per 100 person-years) in Taiwanese students reported by Beasley et al. (22), much higher than the incidence among military personnel in Italy (0.024 per 100 person-years) reported by D’Amelio et al. (23), and even higher than reported incidences in high-risk groups of injection drug users in Switzerland, Australia, and Denmark (24–26).

Proportion of chronic carriers

Earlier studies have shown an inverse correlation between age and risk of chronic infection (5, 22, 27). Among the Yup’ik in Alaska, McMahon et al. (8) found that the overall proportion of HBV-infected persons who became chronically infected was 13.3%, decreasing from 28.6% among 0–4-year-old children to 8.4% among subjects 10 years of age or older. However, in the present study, infection among adults led to a higher proportion of chronically infected participants, as approximately 17.5%–22.7% of those infected between 15 and 44 years of age were estimated to become chronic carriers.

In self-limited HBV infection, the cellular immune response clears viral infection. The probability that chronic infection will develop is inversely related to the rate of jaundice during acute infection (28). Acute clinical hepatitis is rarely seen in Greenland (16). It might be that Greenlanders do not recognize and react to the virus to the same extent that other populations do; hence, a higher fraction of the population becomes chronically infected. Furthermore, in Asia (1–4, 28), Alaska (8, 29, 30), and Africa (2), the majority of chronic carriers have been infected before the age of 15 years. In Greenland, susceptible individuals rarely encounter the virus before early adulthood. We investigated morbidity and mortality in HBV carriers and found that the standardized incidence rates of chronic hepatitis, cirrhosis, and hepatocellular carcinoma were lower than among HBV carriers in other population-based cohorts (31). Thus, the results seem to indicate that chronic HBV carriage in Greenland causes less morbidity than does chronic HBV carriage in other populations. Factors that affect the balance between immune control of HBV infection and immune-induced liver injury could play a particular role in the natural history of HBV infection in Greenland. Further studies on the interaction between hosts and HBV virus in Greenland are warranted to elucidate whether particular genetic or other factors that have an effect are present.

In countries in which it is lowly endemic, HBV infection mainly takes place in adulthood, but only a small fraction of infected persons become chronic carriers and thus prone to transmit HBV. In the present study, infection occurred mainly in adulthood, and yet a high proportion of subjects became chronic carriers and therefore infectious. Studies in various populations have shown that risk factors for HBV infection in adulthood include injection drug use, a high number of sexual partners, a long duration of sexual activity, and a history of sexually transmitted infections (32). Injection drug use is extremely rare in Greenland (K. Ladefoged, Department of Internal Medicine, Dronning Ingrid’s Hospital, personal communication, 2013), but Greenland has very high rates of sexually transmitted infections, including chlamydia (incidence of 5,543 per 100,000 persons in 2006) as compared with those in Scandinavian countries and other Inuit populations in the Arctic (33). Studies of sexual behaviors in Greenland in the 1980s and 1990s indicated a high lifetime number of sexual partners (34, 35). Gesink et al. (36) recently interviewed 314 Greenlanders with median age of 23 years (range, 15–65 years) about their sexual experiences. Among 293 participants, the median age at first sexual intercourse was 15 years (range, 9–22 years), and the median lifetime number of sexual partners up to the time of interview was 7 female partners for men (range, 0–125 partners) and 13 male partners for women (range, 0–320 partners). Given the high rate of subjects who carry HBsAg, it is conceivable that sexual transmission accounts for our findings of high rates of HBV transmission among 15–24-year-old subjects. Thus, it seems that the high HBV transmission rate in adolescence and adulthood, as well as the high proportion of chronic carriers, could account for the high HBV prevalence in Greenland.

HBsAg seroclearance

Annually, we found that 0.83% of infected subjects had spontaneous HBsAg seroclearance. This is in line with other studies in which approximately 0.5%–1% of chronic carriers had HBsAg seroclearance (7, 37, 38). The mean age at seroclearance in the present study was 44 years. This is in line with results from studies from Asia in which the mean/median age of seroclearance was between 48 and 54 years of age (10, 39–41). However, comparisons between studies are difficult because the differences observed in the studies might be caused by differences in the mean ages of participants and the length of follow-up (38, 42). Because Asian chronic carriers are usually infected perinatally or in early childhood, seroclearance in Asia occurs on average after 40–50 years of infection. In Greenland, the chronic carriers are most likely to be infected in early adulthood, and seroclearance occurs 20–30 years after infection. Furthermore, the cumulative probability of HBsAg seroclearance in Greenland is 50% by 75 years of age, which is of the same magnitude as the probability found in a study from Taiwan (43). Hence, Greenlandic chronic carriers have the same average age and cumulative probability of seroclearance as chronic carriers perinatally infected in Asia.
infected in adulthood usually seroconvert and become positive for the hepatitis B envelope antibody shortly after infection, whereas persons infected perinatally might remain in the immunotolerant phase (e.g., hepatitis B envelope antigen positive with a high viral load) up to 30 years after infection (44). Thus, the time to HBsAg seroclearance might be related to sustained inactive hepatitis (i.e., HBV DNA concentrations <2,000 IU/mL, normal alanine aminotransferase, hepatitis B envelope antibody–positive) for a longer period of time (20–30 years) rather than age at infection (7, 39, 45, 46).

Most studies have found no difference in HBsAg seroclearance rates by sex, although controversy exists (39, 47). However, in the present study, a significantly higher proportion of female subjects younger than 50 years of age cleared HBsAg as compared with same-aged male subjects, whereas there was no difference between sexes for participants 50 years of age or older. Among Alaskan Natives, including the Yup’ik, a higher proportion of female participants also cleared HBsAg (47), but in a study from Taiwan, HBsAg seroclearance was somewhat higher among men (39). However, we found no sex difference in the mortality ratio between chronically infected and HBV-negative persons (data not shown). Thus, differences in mortality rates cannot explain the sex difference in HBsAg clearance rates.

Strengths and limitation

Strengths of the present 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, which is updated on a daily basis, and information on longitudinal HBV status was based on linkage with other registries using the unique personal identification number. This minimized bias due to selection of participants and loss to follow-up. However, a higher fraction of women, as well as of inhabitants from areas with lower rates of HBsAg prevalence, participated in the population-based surveys in 1987 and 1998. Comparing the prevalence with and without adjustment for the differential participations rates revealed that bias related to this issue was most likely small.

Vaccination against HBV was not included in the childhood immunization program until 2010. From 1992 to 2010, HBV prevention relied on vaccination of at-risk infants born to HBsAg-positive mothers. However, the program was ineffective (48). Hence, Greenland has until now been HBV vaccination naïve, as indicated by an outbreak of HBV and hepatitis D virus among children from 2006 to 2010 (49). Chronic carriage is usually defined as having 2 HBsAg-positive test results separated by 6 months (50). We based the estimation of HBV chronic carriage on a single HBsAg-positive test. We acknowledge that this could lead to the inclusion of some persons newly infected with HBV who would overcome the infection and become immune. However, in an acute self-limited infection, HBsAg will be present for only 2–3 months (50, 51). Thus, we consider this possibility likely to have a negligible impact in a population-based survey of apparently healthy persons, the resulting bias of which would mean that the true association is stronger than the one observed. We characterized HBcAb-positive/HBsAg-negative individuals as immune even though a small proportion could be HBcAb-positive only due to loss of either hepatitis B surface antibody or HBsAg. However, the resulting bias would lead to overestimation of the number of subjects who were immune, and thus the true association would be stronger than the one observed. Furthermore, the statistical approach is based on the assumption of similar mortality rates in infected (chronic carriers and immune) and noninfected (HBV-negative) subjects. This is approximately true because of the high proportion of immune persons among those who are infected, but with a higher mortality rate in chronic carriers, the estimated proportion of chronic carriers among infected might have been underestimated. To our knowledge, the present study has a longer follow-up time for estimating the rate of HBsAg seroclearance among chronic carriers than any previous study. The higher mortality among chronic carriers might have led to some overestimation of the HBsAg seroclearance.

Conclusions

In the present study, we reported the incidence of HBV infection, the proportion of chronic carriers, and the rate of HBsAg seroclearance in a population-based cohort of 8,879 persons in Greenland. In contrast to countries in Asia and Africa in which HBV is highly endemic, in Greenland, HBV transmission among the Inuit appears mainly to occur in young adulthood or later. HBV infection seems to lead to a higher proportion of chronic carriers among persons infected in adulthood (17.5%–22.7%) than reported elsewhere. This high fraction of chronic infection could be a factor in maintenance of the high HBV transmission rates despite very little HBV transmission in childhood among Greenlanders. The rate of HBsAg seroclearance was of same magnitude (0.89% per year) as that in other longitudinal studies and therefore does not seem to explain the high prevalence of chronic infection among Greenlanders.

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APPENDIX

The age-specific incidence of hepatitis B virus (HBV) infection was estimated by regarding the ages at testing as interval-censored time-to-infection data. The cumulative risk of infection by age was estimated based on these interval-censored data using a Turnbull estimator in PROC LIFEREG in SAS (SAS Institute, Inc., Cary, North Carolina). The age-specific incidence of infection in the interval between ages $a_1$ and $a_2$ was approximated from the estimated cumulative risk by $-(C(a_2) - C(a_1))/(a_2 - a_1)$ divided by $C(a_1)$, with $C(a)$ being the estimated cumulative risk at age $a$. The 95% confidence intervals of the age-specific incidence were calculated using age-specific standard errors that were estimated by boot-strapping 100 samples from the cohort. In the estimation of the cumulative risk, nonchronic test results (e.g., those that were negative for hepatitis B surface antigen (HBsAg)) were replaced by negative or immune test results using imputation. The imputation was based on age-specific test result history and the estimated cumulative risk of immunity when ignoring nonchronic test results.

We estimated the age-specific incidence of HBV infection with subsequent chronic carriage in a similar way. In those analyses, persons were considered to be immune from the midpoint between their most recent HBV-negative test and the first immune test during follow-up. The ratio of the incidence of chronic carriage to the incidence of HBV infection in a given age-group was interpreted as the proportion of chronic infections among persons who became infected in that age group. The 95% confidence interval of the ratio was estimated by bootstrapping as described above.

The HBsAg seroclearance rate was estimated among chronic carriers who had at least 1 test result subsequent to the first positive antigenemia test. Because the data only contained information on whether HBsAg seroclearance had occurred between 2 tests, the HBsAg seroclearance rate was estimated using an approach similar to that used to estimate the incidence of HBV. HBsAg clearance was defined as the persistent absence of HBsAg in a person who had previously been a chronic carrier for at least 1 year previously (45). Persons with a negative HBsAg test within a year of the first positive HBsAg test were therefore considered immune, because the antigenemia might have arisen from an acute infection. Thus, only test results from more than 1 year after the first positive antigenemia result were used in the estimation. HBV incidence and HBsAg seroclearance rates stratified by age and sex were compared using inverse variance-weighted linear regression, with the age- and sex-specific estimates weighted by the inverse of the square of their standard errors of the estimates.