Hepatitis B and C virus infection and risk of pancreatic cancer: A population-based cohort study (JPHC Study Cohort II)

Running title: hepatitis virus and risk of pancreatic cancer

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Conflict of Interest
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Abstract

Background: The aim of this study was to assess the association between HBV and HCV and the risk of pancreatic cancer among Japanese adults.

Methods: 20,360 subjects of the Japan Public Health Center-based prospective Study Cohort II with available data on HBV and HCV infection status from blood samples were followed up until the end of 2010 for an average of 16 years. Cox proportional hazards models were employed to calculate hazard ratios (HRs) and 95% confidence intervals (95%CIs).

Results: During 324,394 person-years, 116 newly diagnosed cases of pancreatic cancer were identified. Compared to individuals without a positive infection marker, the multivariate-adjusted hazard ratios were 1.22 (95% CI, 0.81-1.84) for anti-HBc and 0.69 (95% CI, 0.28-1.69) for anti-HCV. There were no pancreatic cancer cases among HBsAg positive participants.

Conclusion: In the JPHC Study we did not observe a statistically significant association between Hepatitis B or C and the risk of pancreatic cancer.

Impact: Our results do not support an association between Hepatitis B or C and the risk of pancreatic cancer.

Introduction

A recent meta-analysis including studies conducted in China, South Korea, Taiwan and the United States found chronic hepatitis B and C virus infection increased the risk of pancreatic cancer (1). Another Taiwanese study found null results (2). The status of HBV and HCV infection is different between Japan and other countries. The aim of this study was to for the first time in Japan assess the association between chronic infection of hepatitis virus and pancreatic cancer.

Keywords: hepatitis B virus; hepatitis C virus; pancreatic cancer; cohort study; Japan
pancreatic cancer risk in the Japan Public Health Center-based prospective Study (JPHC Study).

Materials and methods

Details of the study design (3), questionnaire, blood check up and laboratory analysis and follow-up information have been detailed in a previous paper (4). The study protocol was approved by the Institutional Review Board of the National Cancer Center, Japan (Approval number: 13-021, 16-59). We restricted subjects to those who responded to the questionnaire and provided their blood ($n=20,887$). We further excluded those with unavailable data on HCV and HBV infection status from the blood samples ($n=68$) and those with a history of cancer ($n=459$). Finally, a total of 20,360 individuals were included in the present analysis. Details of cancer incidence identification have also been described elsewhere (4). A total of 116 incident cases pancreatic cancer cases (C25) were identified.

Plasma samples were screened for hepatitis B virus antigen (HBsAg) by reversed passive hemagglutination (R-PHA). Antibodies against hepatitis B core antigen (anti-HBc) were analyzed by passive hemagglutination (R-PHA) with a commercial kit common in Japan. For anti-HCV antibody (anti-HCV) a third-generation immunoassay was applied (4).

Person-years of follow-up from the date of baseline survey were calculated until the date of diagnosis of pancreatic cancer, date of death, move from the public health center area, or December 31st 2010, whichever occurred first. Statistical analyses were performed using STATA - version 13 (STATA Corporation, College Station, TX, USA). Multivariate-adjusted hazard ratios (HR) and corresponding 95% confidence interval (95%CI) of pancreatic cancer were calculated for HBsAg, anti-HBc, and anti-HCV by Cox proportional hazards model. In Model 1 we adjusted for sex, year of age at baseline (40-44, 45-49, 50-54, 55-59, 60-64, 65-69) and study area (six areas treated as strata). In Model 2 we additionally adjusted for body mass index (<25.0 kg/m$^2$, 25.0-26.9 kg/m$^2$, $\geq$27.0 kg/m$^2$), diabetes (yes, no) and
smoking status (never, former, current). In Model 3 we replaced follow-up time with age as the time scale due to the strong association with pancreatic cancer risk.

Results

Among 20,360 participants 116 pancreatic cancer cases were identified after a mean follow-up of 16 years (324,394 person years). Basic study characteristics have been reported by Abe and colleagues (4). Hepatitis B and C were not statistically significantly associated with the risk of developing pancreatic cancer. Compared to individuals without a positive infection marker, the multivariate-adjusted hazard ratios were 1.22 (95% CI, 0.81-1.84) for anti-HBc and 0.69 (95% CI, 0.28-1.69) for anti-HCV (Table 1). There were 0 pancreatic cancer cases among participants with a positive HBsAg marker.

Discussion

We did not observe a significant association between anti-HBc, a marker for past HBV exposure, and anti-HCV antibodies and the risk of pancreatic cancer in this large Japanese population-based cohort study. This study did not find cases among HBsAg positive, hepatitis B positive, HBV carrier, subjects. In contrast to our study, a previous meta-analysis, predominantly case-control studies in other Asian countries found HBsAg and anti-HCV antibodies increased the risk of pancreatic cancer (1). Additional studies in Korea and Sweden also suggested anti-HCV antibodies could be associated with an increased risk (5, 6), while a recent study in Taiwan found null results for all antibody variations (2).

Established risk factors of pancreatic cancer such as tobacco smoking, chronic pancreatitis, obesity and diabetes account for <50% of cases (7). Some mechanisms have been proposed by Michaud (8). Inflammation is critical in the development of pancreatic carcinogenesis but the causes other than pancreatitis are unclear. Michaud postulates that infections may influence tumor progression rather than initiation. Anti-HBc-positive status,
the sero biological marker of past exposure to HBV had an increased risk of developing pancreatic cancer.

Strengths and limitations to the study have been described by Abe and colleagues (4). Briefly, strengths include the large sample, high response rate and low loss to follow-up and relatively long years of follow-up. Limitations include the mainly non-metropolitan population, relatively limited number of pancreatic cancer cases, the voluntary nature of the blood samples, the lack of potential exposures related to HBV and HCV in the survey, and not combining anti-HBc and HBsAg in HBV infection due to the concept of seroconversion.

Further research, especially for HBsAg is needed to confirm our results. Particularly regional pooled analysis of cohort studies may be useful due to the relatively small number of cases per positive infection marker.

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References


Table 1 Association between hepatitis virus infection and pancreatic cancer (JPHC Cohort II: 1993-2010)

<table>
<thead>
<tr>
<th>Infection Marker</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Anti-HBc (n=11,042)</td>
<td>116</td>
<td>66</td>
<td>56.9</td>
</tr>
<tr>
<td>Anti-HCV (n=1,129)</td>
<td>116</td>
<td>5</td>
<td>4.3</td>
</tr>
</tbody>
</table>

Sample=20,360; Total person-years=324,394; HBsAg (n=508)=0 cases

n: Number of cases among positive infection marker; %: Prevalence of cases among positive infection marker; HR: Hazard ratio

Model 1: adjusted for sex, age, and study area (treated as strata); Model 2 additionally adjusted for BMI, diabetes and smoking; Model 3 attained age as the time scale.
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