

RESEARCH COMMUNICATION

Chronic Hepatitis B Virus Infection and Pancreatic Cancer: A Case-control Study in Southern China

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Abstract

Background: The association of hepatitis B virus (HBV) infection and pancreatic cancer is still controversial. The purpose of this study is to determine whether chronic HBV infection increases the risk. **Methods:** In this case-control study, there were 1,066 patients recruited, with 533 in the study group and 533 controls, frequency-matched for age and sex. Blood samples were collected to detect hepatitis viral infection. **Results:** Compared to 77 patients (14.4%) in the control group, 80 pancreatic cancer patients (15.0%) were seropositive for HBV surface antigen (not statistically significant, $P=0.8$). The prevalence of HBV e antigen was higher in study group than that of control group ($P=0.03$). Further analysis indicated that HBeAg was a risk factor for pancreatic cancer (OR=2.935, 95% CI: 1.048-8.220). **Conclusions:** In HBV endemic area of China, there appears to be no significant association between chronic HBV infection and pancreatic cancer, but the role of HBeAg needs further exploration.

Keywords: Hepatitis B Virus - pancreatic cancer - hepatitis C virus - case-control study - HBeAg

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Introduction

Hepatitis B virus (HBV) has caused worldwide public health problems, especially in China. It is estimated that more than 2 billion people in the world were previously exposed to HBV, and more than 350 million of them are chronic carriers (WHO, 2008). As a result, 600,000 deaths approximately can be attributed to HBV associated disease such as hepatocellular cancer and liver cirrhosis by annual incidence (Shepard et al., 2006; Caldwell and Park, 2009). The prevalence of HBV infection in China is up to 7.18%, which means more than 90 million Chinese are infected.

HBV has a strong preference for liver cells and is interrelated to hepatocellular cancer consequently. Although the virus can be found in some extrahepatic organs such as kidney and pancreas, it was not originally considered that the virus contributed to carcinogenesis of these ones (Ganem and Prince, 2004). However, some recent studies reported that there was relationship between pancreatic cancer and infection with HBV (Hassan et al., 2008; Iloeje et al., 2009).

Provided their intimate relationship in anatomy and common blood supply shared by liver and pancreas, it's reasonable to presume that HBV could mislocate in pancreas. In fact, HBsAg and HBV DNA were detected in pancreatic juice and tissue several decades ago (Hoefs et al., 1980; Yoshimura et al., 1981; Dejean et al., 1984). Viral penetration and multiplication in pancreatic cells might lead to further injuries. Some studies demonstrated that

pancreatic enzyme elevated in chronic hepatitis patients (Katakura et al., 2005). Moreover, higher level of HBsAg was detected in tissue specimens of pancreatic carcinoma and chronic pancreatitis (Hohenberger, 1985).

Although these previous studies suggested that HBV might play a role in the development of pancreatic cancer, the information we can refer to is limited currently. The purpose of this study is to explore whether chronic HBV infection would increase the risk of pancreatic cancer.

Materials and Methods

Patients

This study is a multi-centre, case-control study. From January 1997 to September 2008, patients treated in two hospitals in Southern China (the First Affiliated Hospital of Sun Yat-sen University and Cancer Center of Sun Yat-sen University) were screened to recruit. The inclusion criteria of study group were as follows: pancreatic cancer confirmed by histology or diagnosed by symptoms, signs and more than two types of imaging tools; age of 16 years or older; no other malignancy coexisted. Patients in the control group were chosen randomly in the patients from orthopedics department and neurology department in the same hospitals. Patients in case and control groups were frequency-matched by age (± 5 years) and sex. The study was conducted in accordance with the ethics principles of the Declaration of Helsinki. Written informed consent was obtained from all patients.

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Viral infection testing

Blood samples were collected from patients before treatment. Enzyme-linked immunosorbent assay was used to test for the presence of HBsAg, hepatitis B antibody (anti-HBs), anti-HBc, hepatitis B e antigen (HBeAg), hepatitis B e antibody (anti-HBe), hepatitis A antibody (anti-HAV), hepatitis C antibody (anti-HCV), hepatitis D antibody (anti-HDV), hepatitis E antibody (anti-HEV). The researchers running these assays were blinded for the subjects. Uncertain results should be reconfirmed at an outside laboratory (Kingmed Diagnostics, Guangzhou, China).

Chronic HBV infection was defined by the presence of HBsAg, and appearance of anti-HBs signifies the recovery of HBV infection or immunized with vaccine (Lee, 1997). HBeAg was considered as an indication of high titers of HBV in the blood, and seroconversion to anti-HBe was a marker of circulating viral load reduction (Ganem and Prince, 2004). Detection of anti-HBc but negative for HBsAg and anti-HBs was a evidence of past exposure to HBV (Lee, 1997). Chronic HCV infection was defined by the presence of anti-HCV (Pawlotsky et al., 1998).

Statistical analysis

Sample size was estimated under the presumption that infection rates in control and study group are 10% and 16% respectively according to prior studies, and the power to detect this difference is 80% with 5% level of significance. According to these parameters, 1000 patients were needed at least. Student's t-test was used to compare means of age and Chi-square tests were used to compare proportions between the two groups. Unconditional logistic regression was conducted to explore potential risk factors. SPSS 16.0 for Windows (SPSS Inc., Chicago, IL) was used for all statistical analysis.

Results

At last, there were 1,066 patients recruited, with 533 in study group and 533 in control group. The study:control ratio is 1:1. There were no significant differences in age and sex between the study and control groups (Table 1). The proportion of diabetes in pancreatic cancer patients (n=86, 16.1%) was higher than that in the control group (n=62, 11.6%) with statistically significant difference (P=0.03).

HBsAg was seropositive in 80 cases (15.0%) in the study group and 77 cases (14.4%) in the control group (Table 2). The between-group difference was not statistically significant (P=0.8). The prevalence of HBeAg was significantly higher in the study group (2.6% vs. 0.9%, P=0.03), while the prevalences of anti-HBs (38.1% vs. 61.7%, P<0.0001), anti-HBc (35% vs. 45.2%, P=0.04) and anti-HBe (20.1% vs. 31.5%, P<0.0001) were lower in study group than those in the control group.

The prevalences of anti-HCV and anti-HEV were higher in pancreatic cancer patients than that in the control group, but neither has statistically significant differences (P=0.4, P=0.3). Besides, the prevalences of anti-HAV and anti-HDV had no significant differences between the study and control groups.

To evaluate the risk factors associated with pancreatic

Table 1. Risk Factors for Pancreatic Cancer and Association with Hepatitis Virus Infection (OR(95% CI)

Variable	Univariable	Multiple
HBeAg Positive	2.849 (1.019-7.965)	2.935 (1.048-8.220)
Anti-HCV positive	1.509 (0.533-4.268)	1.592 (0.562-4.512)
Anti-HEV positive	1.814 (0.604-5.448)	1.764 (0.584-5.322)
Diabetes	1.462 (1.029-2.077)	1.464 (1.029-2.083)

cancer further, we employed logistic regression to analyze the data. As shown in Table 1, it was indicated that diabetes (OR=1.464, 95% CI: 1.029-2.083) and HBeAg (OR=2.935, 95% CI: 1.048-8.220) were risk factors for pancreatic cancer. HCV (OR=1.1592, 95% CI: 0.562-4.512) and HEV (OR=1.814, 95% CI: 0.584-5.322) didn't increase the risk of pancreatic cancer statistically.

Discussion

Chronic HBV infection was defined by the presence of HBsAg (Lee, 1997), and its prevalence in both groups were almost the same in our study. The major finding of this study was that there was no significant difference in chronic HBV infection between pancreatic cancer patients and other patients in hepatitis B endemic area of China. This is in accordance with some studies in Korea. A prospective research recruited 201,975 HBsAg positive individuals to follow up for a median of 12 years. As a result, the adjusted relative risk of pancreatic cancer for HBsAg positivity was 1.13 (95% CI: 0.84-1.52), suggesting no association between pancreatic cancer and hepatitis B infection (de Gonzalez et al., 2009). Additionally, a recent case-control study between pancreatic cancer and stomach cancer patients among Koreans also reported a negative result. The odds ratio of HBsAg is 0.90 (95% CI: 0.52-1.56) (Hong et al., 2010).

But some studies reported different conclusions. A prospective cohort study conducted in Taiwan reported that chronic carriers of HBsAg had a significantly high risk of pancreatic cancer, with the HR of 1.95 (95% CI: 1.01-3.78) (Iloeje et al., 2009). There are also some studies which didn't reach clear conclusions. In a retrospective cohort study conducted in the United States, researchers compared the risk of pancreatic cancer development in 28,719 HBV-negative patients, 5,141 previous exposed patients and 404 active infected patients. Univariate analysis showed that prior HBV infection was associated with pancreatic cancer, with a hazard ratio of 1.827 (95% CI: 1.154-2.891). However, in a multivariate analysis that included race, sex, and age, the result was no longer statistically significant (Gordon et al., 2009). Besides, a case-control study in the United States indicated that there was a relationship between the presence of hepatitis B core antibody (anti-HBc) and pancreatic cancer patients showing a hazard ratio of 2.5 (95% CI: 1.5-4.2). But the role of HBsAg was hard to evaluate, because the cases with positive HBsAg was few in this study (Hassan et al., 2008).

The truth is that pancreatic cancer related deaths rank fourth in the United States while the incidence is much lower in China (Hidalgo, 2010; Jemal et al., 2008). Given that HBV infection did contribute to the development of pancreatic cancer, it would be very confusing that the

HBV epidemic countries such as China and Korea have a relatively lower incidence of pancreatic cancer. Therefore, the result of our study is reasonable from this perspective.

Interestingly, we found the prevalence of HBeAg was significantly higher in pancreatic cancer patients, (2.6% vs. 0.9%, $P=0.03$). Further analysis indicated that HBeAg was a risk factor for pancreatic cancers (OR=2.935, 95% CI: 1.048-8.220). HBeAg is a marker of HBV replication, and the seroconversion from HBeAg to anti-HBe is considered as a sign of disease recovery. Some studies have demonstrated that continuous HBeAg detection increases the risk of hepatocellular carcinoma (Yang et al., 2002; Yang et al, 2010). The possible association between HBeAg and pancreatic cancer may lie in similar mechanism: high-titer HBV replication stimulates continuous inflammatory response, which could be a pivotal step of tumor progression (Coussens and Werb, 2002). Nevertheless, the study was not designed for HBeAg and the patients who are seropositive of HBeAg is quite few in both groups of our study especially in the control group, so it is not proper to make conclusions. Moreover, there might be another explanation that HBV reactivation was secondary to oncogenesis considering frequent suppression of immunity function in cancer patient (Oksuzoglu et al., 2002). We also found that the prevalences of anti-HBs, anti-HBe and anti-HBc were even higher in the control group. The reason may lie in suppression of immunity function, either (Oksuzoglu et al., 2002). We will do further research to make it clear.

In this study, we also found that diabetes mellitus was associated with pancreatic cancer significantly with the OR of 1.462(95% CI: 1.029-2.077) which coincided with the reported risk association between pancreatic cancer and diabetes mellitus (Everhart and Wright, 1995). In addition, there have been reports of high frequency of HCV infection in pancreatic patients (Hassan et al., 2008; El-Serag et al., 2009). Similarly, we found that the prevalence of anti-HCV and Anti-HEV was higher in pancreatic cancer patients than that in control group. However, logistic regression didn't identify them as risk factors, and we will increase the sample size to confirm the conclusion in further study.

Our study has some limitations. As a case-control study, the control group came from other patients but not the healthy individuals, allowing the possibility of admission bias. However, the prevalence of HBV in our study was similar with previous report in the same area (Wang et al., 2007), suggesting that control group is qualified to represent the general population of the area. Furthermore, all patients were from HBV endemic district, with the infection prevalence much higher than other district of China, so the result can't represent the situation of the whole country. This problem will be solved in the upcoming prospective study.

In summary, current evidence indicated that there was no significant association between chronic HBV infection and pancreatic cancer. However, the data provided some hints that HBeAg may play a role in the development of pancreatic cancer. This study is the first one to report the relationship between HBV infection and pancreatic cancer in Mainland China and further studies are expected to

confirm our conclusion.

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