BRIEF ARTICLE

Hepatitis B and C viruses are not risks for pancreatic adenocarcinoma

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Abstract

AIM: To investigate whether hepatitis B virus (HBV) and hepatitis C virus (HCV) increase risk of pancreatic ductal adenocarcinoma (PDAC).

METHODS: We recruited 585 patients with cytological and/or pathologically confirmed PDAC in National Taiwan University Hospital from September 2000 to September 2013, and 1716 age-, sex-, and race-matched controls who received a screening program in a community located in Northern Taiwan. Blood samples were tested for the presence of HCV antibodies (anti-HCV), HBV surface antigen (HBsAg), antibodies against HBsAg (anti-HBs), and hepatitis B core antigen (anti-HBc) in all cases and controls. The odds ratio (OR) of PDAC was estimated by logistic regression analysis with adjustment diabetes mellitus (DM) and smoking.

RESULTS: HBsAg was positive in 73 cases (12.5%) and 213 controls (12.4%). Anti-HCV was positive in 22 cases (3.8%) and 45 controls (2.6%). Anti-HBs was positive in 338 cases (57.8%) and 1047 controls (61.0%). The estimated ORs of PDAC in multivariate analysis were as follows: DM, 2.08 (95%CI: 1.56-2.76, $P < 0.001$), smoking, 1.36 (95%CI: 1.02-1.80, $P = 0.035$), HBsAg$^+$/anti-HBc$^+$/anti-HBs$^-$, 0.89 (95%CI: 0.89-1.68, $P = 0.219$), HBsAg$^-$/anti-HBc$^+$/anti-HBs$^+$, 1.03 (95%CI: 0.84-1.25, $P = 0.802$).

CONCLUSION: HBV and HCV infection are not associated with risk of PDCA after adjustment for age, sex, DM and smoking, which were independent risk factors of PDAC.

Core tip: Previous studies on hepatitis B virus (HBV) status and pancreatic cancer risk have produced conflicting results. This study is the first study to use controls from the general population compared to previous hospital-based case-controls studies with age- and sex-matched controls. HBV infection was determined by measuring antibodies against hepatitis B core antigen and HBV surface antigen. The risk of HBV/hepatitis C virus infection was evaluated after adjustment for im-

portant risk factors such as age, sex, diabetes mellitus and smoking in a high-endemic HBV area.

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignant tumors with an average 5 year survival rate of < 5%. Early diagnosis followed by surgery with curative intent is the only way to improve the outcome of PDAC. Diabetes mellitus (DM), smoking, chronic pancreatitis, and family history of PDAC are well known risk factors of PDAC[1]. Screening high-risk individuals for PDAC might shed some light on detection of the early stage of the disease.

Several studies on hepatitis B virus (HBV) status and pancreatic cancer risk have produced conflicting conclusions[2-6]. The previous studies were conducted with a different design and population in regions with different HBV or hepatitis C virus (HCV) prevalence rate. The prevalence of HBV and HCV infection varies widely among different regions of the world, ranging from < 0.5% in western countries to 8%-25% in endemic countries in East Asia[7,8]. HBV or HCV infection is a global challenge[9] and it is nowadays regarded as a major risk for hepatocellular carcinoma (HCC)[8]. In Taiwan, a HBV-endemic area with about 15% carrier rate, chronic HBV infection has the strongest association with the development of HCC and accounts for 75%-80% of all HCC cases[8,10,11]. Besides, an association between HBV or HCV infection and extrapancreatic cancers has been reported in non-Hodgkin's lymphoma[12]. One study from the United States has demonstrated that past exposure to HBV may be associated with pancreatic cancer development[2] with low prevalence of chronic HBV or HCV infections (< 2%)[13]. Studies from an HBV-endemic area have shown contradictory results[4,5]. A cohort study by Iloeje *et al*[14] conducted in Taiwan suggested that chronic HBV carriers had an increased risk of pancreatic cancer, with an adjusted hazard ratio of 1.95 (95%CI: 1.01-3.78). However, only about 69% of cases of pancreatic cancer were proven histologically to be adenocarcinoma. Furthermore, the incidence rate of pancreatic cancer in that cohort was 12.7 cases/100000 persons, even among those without hepatitis B infection (20.4 cases/100000 person among those with hepatitis B). In fact, the officially reported incidence rate of pancreatic cancer in Taiwan was 2.15-6.18 cases/100000 persons in the same period during the REVEAL-HBV cohort study, provided by Health Promotion Administration, Ministry of Health

and Welfare, http://www.hpa.gov.tw/. More importantly, the REVEAL-HBV cohort study did not adjust for DM. DM is a well-known risk factor for PDAC and accounted for about two times the risk, which might have confounded their result. The REVEAL-HBV cohort study gave an odds ratio (OR) of 1.95, which meant that those with hepatitis B were about twice as likely to develop pancreatic cancer as those who were not infected. However, only a small increase in absolute risk, about 0.08%, was observed in the REVEAL-HBV cohort study[15]. It is mandatory to validate the association of HBV infection in histologically proven PDAC with adjustment for important risk factors including DM and smoking.

Taiwan is an endemic area of HBV infection with a prevalence of about 15%[8,10,11]. The prevalence and incidence of PDAC in Taiwan (http://www.hpa.gov.tw/) are lower than in the United States[1]. It is important to know whether there is an association between HBV infection and PDAC in HBV-endemic areas because it could influence the attitude and strategy to screening for PDAC. Therefore, we conducted a large case-control study to evaluate whether HBV and HCV infections are possibly associated with histologically proven PDAC in Taiwan, with adjustment for known risk factors.

MATERIALS AND METHODS

Study population
Cases were patients with histologically or cytologically proved PDAC in National Taiwan University Hospital between September 2000 and September 2013. Controls were individuals recruited from a free screening program in a community located in Northern Taiwan supported and sponsored by the Liver Disease Prevention and Treatment Research Foundation. A total of 1716 age-, sex- and race-matched controls were randomly selected from 6000 individuals who participated in the screening activity. The patients and controls were frequency matched by age and sex in a narrow-confined area in Taiwan, which was considered to have the same ethnicity (Taiwanese). The study was approved by our Institutional Review Board. All the cases and controls were born before the launch of the vaccination program for HBV in Taiwan[16].

Serology and definition of HBV and HCV infection
Blood samples were collected from patients and controls. Serum samples were tested for aspartate aminotransferase, alanine aminotransferase, HCV antibodies (anti-HCV), HBV surface antigen (HBsAg), antibodies against HBsAg (anti-HBs), and antibodies against HBV core antigen (anti-HBc) (General Biologicals Corporation, Hsinchu, Taiwan)[17]. Anti-HBs was considered positive if the titer was ≥ 10 mIU/mL. The laboratory researcher running these assays was blinded to the disease status (cases or controls) of the participants' blood samples. Blood samples were drawn from patients with pancreatic cancer before treatment (operation or chemotherapy). HBV

infection was defined by the presence of HBsAg. Positivity of anti-HBs confers protective immunity and was detectable in patients who recovered from HBV infection or were immunized with HBV vaccine[16,18]. Patients who were positive for anti-HBc were defined as previously exposed to HBV. Individuals with chronic HCV infection were defined as those with positive HCV antibodies[19].

Statistical analysis

Statistical analysis was performed by SPSS version 17 (SPSS, Chicago, IL, United States). We compared the demographic characteristics among patients and controls. The t test was used to compare the mean age between patients and controls. The χ^2 test was used to compare proportions. We performed multivariate unconditional logistic regression analyses using all variables significant at $P < 0.05$ in the single-factor analyses. For each factor, we calculated the OR and 95%CI using maximum likelihood estimation.

RESULTS

There were no significant difference in age and sex between cases and controls (Table 1). The mean age ($\pm$ SD) for PDAC patients was 63.81 ± 13.73 years and 63.11 ± 8.89 years for controls ($P > 0.05$). Male sex accounted for 51.2% and 53.3% in cases and controls, which did not have a significant difference. About 9% of the controls had DM and 23.4% of the PDAC patients had DM ($P < 0.0001$). Smokers accounted for 14.0% in the controls and 20.0% in the PDAC group ($P < 0.001$) (Table 1).

The prevalence of anti-HCV was not significantly higher among patients with PDAC (3.8%) than in the controls (2.6%) (Table 2). With respect to HBV, HBsAg was detected in 73 (21.5%) and 213 (12.4%) in the PDAC and control groups, respectively, which showed a similar frequency of positivity for HBsAg between the two groups (Table 2). The overall prevalence of anti-HBs with evidence of protective immunity in PDAC and controls was 338 (57.8%) and 1047 (61.0%), respectively. In univariate analysis, HBsAg, anti-HBs and anti-HBc positivity was not associated with an increased risk of PDAC (Table 2).

HBV infection status in a high-endemic area was determined by HBsAg, anti-HBs and anti-HBc, therefore, we further divided the cases and controls into subgroups for further analysis according to the serological markers: HBsAg⁻/anti-HBc⁻/anti-HBs⁻: HBV infection naïve; HBsAg⁺/anti-HBc⁺/anti-HBs⁻: chronic HBV infection; HBsAg⁻/anti-HBc⁺/anti-HBs⁺: past infection with acquired immunity to HBV. In both univariate and multivariate analyses, chronic HBV infection (HBsAg⁺/anti-HBc⁺/anti-HBs⁻) and past infection with acquired immunity to HBV (HBsAg⁻/anti-HBc⁺/anti-HBs⁺) were not associated with risk of PDAC (Table 2).

DM was associated with PDAC in both univariate analysis (OR: 3.08, 95%CI: 2.39-3.97, $P < 0.001$) and multivariate analysis (OR: 2.08, 95%CI: 1.56-2.76, $P <$

Table 1 Characteristics of study population *n* (%)

Characteristics	Cases (*n* = 585)	Controls (*n* = 1716)
Age, yr		
Median	62.00	62.00
mean ± SD	63.81 ± 13.73	63.11 ± 8.89
Sex		
Female	273 (46.7)	837 (48.8)
Male	312 (53.3)	879 (51.2)
DM[b]	137 (23.4)	155 (9.0)
Smoking[a]	117 (20.0)	240 (14.0)

[a]$P < 0.05$, [b]$P < 0.01$ *vs* the control group.

0.001). Smoking was also associated with risk of PDAC in univariate analysis (OR: 1.54, 95%CI: 1.20-1.96, $P = 0.01$) and multivariate analysis (OR: 1.36, 95%CI: 1.02-1.80, $P = 0.035$).

We also stratified the age into two groups, > 50 years and < 50 years. The risk of PDAC was not significantly different in those with or without HBV or HCV infection, regardless of age > 50 or < 50 years.

DISCUSSION

We did not find any positive association between HBV or HCV infection and PDAC after adjustment for age, sex, DM and smoking. This result differed from the previous REVEAL-HBV cohort study[14]. First, in the REVEAL-HBV cohort study, the researchers did not adjust DM as a risk factor, which might have confounded the result. In our study, DM was an independent risk factor for PDAC in multivariate analysis, which increased the risk by twofold. This was similar to previous studies from China and South Korea[4,5,20]. Second, the incidence rate of pancreatic cancer in patients without HBV infection in the REVEAL-HBV cohort study was 12.7/100000 person-years, which was nearly twice the incidence rate officially reported by the Health Promotion Administration, Ministry of Health and Welfare, Taiwan. Not all the PDAC cases in both databases were verified by cytology or histopathology. This observation raises an important issue; namely, that studies from registered databases where the results are not confirmed by histopathology or cytology should be used with care and require verification. With the increased use of abdominal imaging in health checkups, an increase in the number of incidentally found pancreatic neoplasms, such as neuroendocrine tumors and solid pseudopapillary neoplasms, could confound the use of the database if the disease register is not based on histological confirmation. Concern about histologically proven types of pancreatic cancer was also emphasized[3,15].

One recent meta-analysis of HBV or HCV infection and risk of pancreatic cancer described some problems with previous observational studies[21]. They concluded that the findings underscore the need for more studies to confirm this potential relationship[14]. One of the problems came from the selection of controls. The five

Table 2 Pancreatic cancer risk factors and association of pancreatic cancer with hepatitis C virus and hepatitis B virus infection: univariate and multivariate logistic regression analysis

Variables	Cases (*n* = 585)	Controls (*n* = 1716)	Univariate analysis		Multivariate analysis	
			OR	95%CI	OR	95%CI
Hepatitis C						
Anti-HCV[+]	3.8%	2.6%	1.45	0.86-2.43	1.36	0.80-2.31
Hepatitis B						
HBsAg[+]	12.5%	12.4%	1.01	0.86-1.34		
Anti-HBs[+]	57.8%	61.0%	1.14	0.95-1.39		
Anti-HBc[+]	66.0%	66.4%	1.02	0.84-1.24		
HBsAg[-]/anti-HBc[-]/anti-HBs[-]	15.2%	13.6%	1.14	0.88-1.49	1.00	Ref
HBsAg[+]/anti-HBc[+]/anti-HBs[-]	10.3%	12.4%	1.24	0.92-1.68	1.22	0.89-1.68
HBsAg[-]/anti-HBc[+]/anti-HBs[+]	42.7%	41.0%	1.07	0.89-1.29	1.03	0.84-1.25
Age					1.01	0.99-1.02
Male sex	53.3%	51.2%	1.08	0.89-1.30	1.13	0.91-1.40
DM	23.4%	9.0%	3.08[b]	2.39-3.97	2.08[b]	1.56-2.76
Smoking	20.0%	14.0%	1.54[a]	1.20-1.96	1.36[a]	1.02-1.80

[a]$P < 0.05$, [b]$P < 0.01$ *vs* the control group in regression analysis. Blood samples were tested for the presence of anti-HCV, HBsAg, anti-HBs, and anti-HBc in all cases and controls. HBsAg[-]/anti-HBc[-]/anti-HBs[-]: HBV infection naïve; HBsAg[+]/anti-HBc[+]/anti-HBs[-]: chronic HBV infection; HBsAg[-]/anti-HBc[+]/anti-HBs[+]: acquired immunity to HBV infection.

previous case-control studies were all based on hospitalized cases and controls[2,4,20-22]. Therefore, the controls selected from hospitalized patients could not represent the general population. In our study, the controls came from a screening program in Taiwan but not from hospitalized patients or outpatients. The frequencies of HBsAg, anti-HBs and anti-HBc in our controls were similar to those reported in the general population in Taiwan[8,11]. Our study is the first case-control study to address the association of HBV and HCV infection with histologically proven PDAC and with age- and sex-matched controls from the general population.

Cohort studies theoretically might be more informative than case-control studies in terms of design. There were three cohort studies regarding this issue. The first two cohort studies, which did not adjust for DM as a risk factor[14,23], drew a positive conclusion. However, a recent study did not show a significant positive association between HBV infection and pancreatic cancer after adjustment for DM as a risk factor[6]. To the best of our knowledge, DM is a risk factor of pancreatic cancer with an average OR of about 2[1]. Whether the association of DM, HBV infection and PDAC was the same as in the previous two cohorts awaits our attention.

We defined HBsAg[-]/anti-HBc[-] as "never exposed to HBV", and HBsAg[-]/anti-HBc[+] as "past exposure to HBV". In a relatively low-prevalence region in the United States, only 1/879 (0.1%) controls were HBsAg[+], 20/879 (2.3%) were anti-HBs[+], and 54/879 (6.14%) were anti-HBc[+]. In our study, the positive frequency of HBsAg, anti-HBs and anti-HBc was 12.4% (213/1716), 61.1% (1048/1716) and 66.4% (1140/1716) in our controls. Besides, all negative serology markers (HBsAg[-]/anti-HBc[-]/anti-HBs[-]) was considered seronegative for HBV infection in Taiwan rather than only HBsAg[-]/anti-HBc[-][18,24]. It was more appropriate to do subgroup analysis including all these three serology markers (HBsAg, anti-HBc and anti-HBs) simultaneously to calculate the risk of HBV in

PDAC in a high-endemic area. In the analysis by El-Serag *et al*[23] from the United States, only the cohort studies included all three of these markers. They did not stratify DM as a risk factor, which could have confounded the results because the study was in a region with a low prevalence of HBV and high incidence of pancreatic cancer. Three case-control studies have taken anti-HBc into consideration in their analysis. All three came from hospital-based population in an HBV-endemic area but with conflicting results[4,5,22]. Only one of these studies concluded that HBV was a risk factor for pathologically confirmed PDCA after adjustment for DM[4]. The other two studies showed contradictory results and neither of them adjusted for factors such as DM and smoking.

Our study is believed to be the first to address the association between HBV/HCV infection and PDAC in a high-endemic HBV area by using population-based controls and histopathologically or/and cytologically confirmed PDAC, with adjustment for age, sex, DM and smoking. We showed that HBV or HCV infection was not associated with the development of PDAC. HBV and HCV infections are considered major risk factors for HCC, and HBV accounts for 75%-80% of all HCC cases in Taiwan[8,10,11]. It is reasonable that the incidence of PDAC in Taiwan should be higher if HBV infection is really associated with increased risk of PDAC. According to the National Cancer Registry data, the incidence of HCC in Taiwan is about 30 per 100000 persons in contrast to 7-8 per 100000 persons for PDAC[25]. In our PDAC patients, we did not find any differences in the age at diagnosis with cancer staging, clinical outcome, and survival between patients with or without HBV infection. We also analyzed the hepatitis B e antigen (HBeAg) and anti-HBe status and/or HBV DNA in our PDAC cases who were infected by HBV. There was still no difference between patients with or without HBeAg. It is difficult to understand the biological explanation for PDAC risk in patients with HBV infection. In the meta-analysis, posi-

tive HBeAg was not a risk factor for pancreatic cancer, in contrast to HBsAg[+] or HBsAg[-]/anti-HBc[+]/anti-HBs[-][21]. The progression from active hepatitis virus infection to chronic inflammatory response in PDAC carcinogenesis is still unknown.

There were some merits to our study. First, we had a good case-control study matched by age and sex. All the PDAC cases were diagnosed with histological and/or cytological confirmation. The risk of HBV infection was evaluated by using HBsAg, anti-HBc and anti-HBs simultaneously with adjustment for DM and smoking. Second, the controls were from the general population and not a hospital-based population. Our controls were from a community taking part in a free hepatitis screening program in Northern Taiwan, which could have represented the normal population better, without selection bias caused by socioeconomic differences in recruitment, such as control data from those taking part in paid health checkups.

Our study had some limitations. It was a retrospective case-control study. The reported risks of pancreatic cancer such as family history and body mass index[1,26] could not be obtained in our controls because the aim of the screening campaign was for detection of HBV and HCV infection. In determining the HBV status, we could now examine the HBV DNA to clarify the HBV status more clearly. Analysis of viremia is more accurate to determine HBV status compared to serological markers. Only some of our PDAC patients were checked for HBV DNA. Our study could not establish whether the viral load increased the risk of PDAC.

In conclusion, our study is believed to be the first to address the association of HBV and HCV infection with histologically proven PDAC in an endemic area of Taiwan, with controls coming from the general population. HBV and HCV infection was not associated with the risk of PDAC. The exact role and association of risk of HBV infection and PDAC awaits further studies conducted in other endemic and non-endemic areas, with adjustment for well-documented risk factors of PDAC.

COMMENTS

Background
Previous studies on hepatitis B virus (HBV) status and pancreatic cancer risk have produced conflicting results.

Research frontiers
Previous studies have addressed the association of HBV/hepatitis C virus (HCV) with pancreatic ductal adenocarcinoma (PDAC) with some limitations. Some of the analyses did not include important risk factors such as diabetes mellitus (DM) and smoking, which might have confounded the results. Some studies included pancreatic malignancy from databases in which PDAC was not verified by cytology or histopathology. Some of the studies determined HBV status only by the presence of HBV surface antigen (HBsAg).

Innovations and breakthroughs
The present study is believed to be the first to use controls from the general population, compared to previous hospital-based case-controls studies with age- and sex-matched controls. All the PDAC in the study was confirmed by histology and/or cytology. Authors included antibodies against HBV core antigen in addition to HBsAg and antibodies against HBsAg in defining the HBV status. The risk of HBV/HCV infection was evaluated after adjustment for age, sex, DM and smoking in a high-endemic HBV area.

Applications
Negative results in a good quality controlled study are important. It is useful to know whether there is an association between HBV infection and PDAC in endemic area for HBV because it could influence the attitude and strategy to screen for PDAC.

Peer review
The manuscript is well presented and of interest, and the design of this study was appropriate. The study was done well and the results could contribute to our knowledge of this topic.

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