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ORIGINAL REPORT

Association Between Hepatitis B Virus and Pancreatic Cancer

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A B S T R A C T

Purpose
Hepatitis B virus (HBV) and hepatitis C virus (HCV) are considered to be hepatotropic and are a major cause of hepatocellular carcinoma. However, little is known about the role of HBV and HCV infection in other malignancies. This study aimed to determine whether HBV and HCV infections increase the risk for pancreatic cancer development.

Patients and Methods
At The University of Texas M. D. Anderson Cancer Center, Houston, TX, we recruited 476 patients with pathologically confirmed adenocarcinoma of the pancreas and 879 age-, sex-, and race-matched healthy controls. Blood samples were tested for the presence of HCV antibodies (anti-HCV), HBV surface antigen (HBsAg), antibodies against HBV core antigen (anti-HBc), and antibodies against HBsAg (anti-HBs). The positive samples were retested by two confirmatory tests. An unconditional multivariable logistic regression analysis was used to estimate adjusted odds ratios (AORs).

Results
Anti-HCV was positive in seven cases (1.5%) and nine controls (1%). Anti-HBc was positive in 36 cases (7.6%) and 28 controls (3.2%). The estimated AORs and 95% CIs were as follows: anti-HCV–positive, 0.9 (95% CI, 0.3 to 2.8), anti-HBc–positive, 2.5 (95% CI, 1.5 to 4.2), anti-HBc–positive/anti-HBs–positive, 2.3 (95% CI, 1.2 to 4.2), and anti-HBc–positive/anti-HBs–negative, 4 (95% CI, 1.4 to 11.1). Risk modification by past exposure to HBV was observed among diabetics (AOR, 7.1; 95% CI, 1.7 to 28.7).

Conclusion
Past exposure to HBV may be associated with pancreatic cancer development. Should such findings be confirmed by other studies, it may offer important insights into the etiology of pancreatic cancer and may suggest the need to consider prevention of HBV reactivation among patients with HBV-related pancreatic cancer during chemotherapy.

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INTRODUCTION

Infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) is a major global public health problem,[1,2] with a wide spectrum of clinical manifestations. The prevalence of HBV and HCV infection varies widely among different parts of the world.[3,4] In the United States, the prevalence of chronic HBV or HCV infection is estimated to be less than 2%.[5] HBV and HCV are considered to be hepatotropic and are significantly associated with end-stage chronic liver diseases, including hepatocellular carcinoma[6] (HCC) and cholangiocarcinoma.[7,8] However, hepatitis is a systemic infectious process, and HBV or HCV viruses may travel through the bloodstream and be deposited in non-liver tissue—for example, kidney, skin, and vessel walls.[9-11] To date, the association between HBV or HCV and extrahepatic cancers has only been studied in non-Hodgkin's lymphoma.[12,13] Other studies investigated the reactivation of HBV infection in patients with cancer undergoing cytotoxic or immunosuppressive therapy.[14-17]

The proximity of the liver to the pancreas and the fact that the liver and pancreas share common blood vessels and ducts may make the pancreas another potential target organ for hepatitis viruses. In fact, hepatitis B surface antigen (HBsAg), a marker for chronic HBV infection, was detected in pure pancreatic juice and bile.[18] This finding was later supported by studies showing evidence of HBV replication in pancreatic cells and concurrent damage to exocrine and endocrine epithelial cells with an inflammatory response.[19,20] The possibility

that viral hepatitis can lead to pancreatic damage was further supported by findings of elevated pancreatic enzyme levels in a substantial percentage of patients with acute and chronic HBV and HCV infection.[21,22]

Although it seems reasonable that hepatitis virus infection may cause pancreatic injuries, to our knowledge, no previous studies have been conducted to investigate the possible association between viral hepatitis and pancreatic cancer. Therefore, we embarked on the present large-scale, case-control study to evaluate whether HBV and HCV are possibly associated with pancreatic cancer development.

PATIENTS AND METHODS

Study Population

The study was a part of an ongoing hospital-based, case-control study conducted at The University Texas M. D. Anderson Cancer Center.[23,24] The study was initiated in January 2000, and a total of 1,144 cases and 1,072 controls have been recruited by the end of May 2007. Cases were patients with newly diagnosed pancreatic adenocarcinoma who were evaluated and treated at the Gastrointestinal (GI) Center of M. D. Anderson. The inclusion criteria were as follows: pathologically confirmed diagnosis of pancreatic ductal adenocarcinoma, United States residency, and ability to communicate in English and to donate a blood sample. The exclusion criteria were the presence of other types of pancreatic disease, such as neuroendocrine tumor, adenomas, cysts, or unknown primary tumors; concurrent cancer at another organ site; and past history of cancer.

Controls were healthy individuals recruited from patient companions at M. D. Anderson. They were friends and genetically unrelated family members (spouses and in-laws) of patients at our institution who had cancers other than pancreatic, GI, lung, or head and neck cancer (smoking-related cancers). The eligibility criteria for controls were the same as those for patients, except for the cancer diagnosis. The patients and controls were frequency matched by age (± 5 years), race, and sex. All participants were personally interviewed for demographic characteristics and potential risk factors for pancreatic cancer. No proxy interviews were conducted. The study was approved by M. D. Anderson's institutional review board, and all participants signed informed consent documents for participation. A detailed description of the study population and study conduct was previously published.[23,24]

HBV and HCV Testing

Blood samples were collected from patients and controls. Plasma samples were separated and tested for the presence of HCV antibodies (anti-HCV) using a third-generation enzyme-linked immunosorbent assay (Abbott Laboratories, North Chicago, IL). The samples were also tested for the presence of HBsAg and antibodies to hepatitis B core antigen (anti-HBc) and HBsAg (anti-HBs) using the enzyme-linked immunosorbent assay. The laboratory researcher running these assays was blinded for the disease status (cases or controls) of the participants' blood samples. Positive results prompted a repeated confirmatory testing at the GI laboratory facility at M. D. Anderson. A second confirmatory test of the positive samples was performed at an outside laboratory (University of Texas School of Public Health, Houston, TX). Blood samples were drawn from patients with pancreatic cancer before chemotherapy (70%) or during follow-up visits (30%).

Three participants (two cases and one control) were anti-HBc–positive for the initial test, anti-HBc–negative for the first confirmation test, and borderline positive for the second confirmatory test (absorbance titer was slightly larger than the cutoff value of Abbott laboratories). Accordingly, we repeated our statistical analysis by including and excluding them from the pool of anti-HBc–positive participants. The final status of anti-HBs was missing for one control because of insufficient plasma sample.

Chronic HBV infection was defined by presence of HBsAg. Clearance of HBsAg from plasma and appearance of anti-HBs were associated with the resolution of acute or chronic HBV infections.[25,26] Therefore, anti-HBs confers protective immunity and is detectable in patients who recovered from HBV infection or were immunized with HBV vaccine. Patients who were positive for anti-HBc but negative for HBsAg and anti-HBs were defined as previously exposed to HBV and possibly harboring persistent HBV infection.[26] Individuals with chronic HCV infection were defined as those with positive anti-HCV antibodies.[27]

Sample Size Consideration and Statistical Methods

We estimated the sample size based on probability of $\alpha = .05$ and $\beta = 0.1$ and assuming that the prevalence of hepatitis virus infection in the control group was 3%[5] and in the cancer group was 7%.[6] A 2:1 control-case ratio was chosen to increase the power of the study. According to these parameters, the estimated sample size was 476 pancreatic cancer cases and 952 healthy controls. From our ongoing study, plasma samples were available for 947 cases and 879 controls. Thus all 879 controls and a computerized random sample of 476 cases were included in the current study. At the time of random case selection, all the clinical parameters of the patients with pancreatic cancer were blinded to the study investigators. Cases and controls were frequency matched by age (± 5 years), sex, and race. STATA software version 9 (STATA Corp, College Station, TX) was used for data management and statistical analysis. We compared the demographic characteristics and proportions of potential risk factors among patients and controls. The t test was used to compare means of age between patients and controls. The χ^2 test was used to compare proportions. We performed multivariable unconditional logistic regression analyses using all variables significant at $P < .05$ in the single-factor analyses. For each factor, we calculated the adjusted odds ratio (AOR) and 95% CI using maximum likelihood estimation. The final model was chosen on the basis of biologic plausibility and lowest −2 log likelihood function.

RESULTS

There were no significant difference between cases and controls in age, sex, educational level, state of residency, and marital status (Table 1). The case-control ratio is 1 to 1.9. The mean age (± standard deviation)

Table 1. Characteristics of Study Population					
	Cases (n = 476)		Controls (n = 879)		
Variable	No.	%	No.	%	P
Age, years					.4
≤ 50	100	21	194	22.1	
> 50	376	79	685	77.9	
Race/ethnicity					.1
White	437	91.8	769	87.5	
Hispanic	20	4.2	68	7.7	
Black	14	2.9	35	4	
Asian	5	1.1	7	0.8	
Sex					.4
Female	177	37.2	347	39.5	
Male	299	62.8	532	60.5	
Education level					.2
≤ High school	154	32.4	260	29.6	
Some college	112	23.5	228	25.9	
≥ College degree	210	44.1	391	44.5	
State of residency					.1
Texas and neighboring states*	327	68.7	644	73.3	
Other states in the United States	149	31.3	235	26.7	
Marital status					.1
Married	422	88.7	806	91.7	
Single	54	11.3	73	8.3	

*Louisiana, Arkansas, Oklahoma, and New Mexico.

for pancreatic cancer patients was 60 ± 10.8 years and for controls was 59.3 ± 10.9 years ($P = .1$).

Multivariable analysis with adjustment for demographic and significant risk factors showed that cigarette smoking, history of diabetes mellitus, and positive family history of cancer were significantly associated with pancreatic cancer development (Table 2).

The prevalence of anti-HCV was not significantly higher among patients with pancreatic cancer (1.5%) than controls (1%). With respect to HBV, HBsAg was detected in one control (.1%). The prevalence of past exposure to HBV (indicated by the presence of anti-HBc) was significantly higher among cases (n = 36; 7.6%) than among controls (n = 28; 3.2%; $P \leq .0001$). The racial distribution of anti-HBc–positive status among cases was as follows: white, 31 patients (6.5%); Hispanic, one patient (0.2%); black, two patients (0.4%); and Asian, two patients (0.4%). The racial distribution of anti-HBc–positive status among controls was as follows: white, 26 patients (3%); Hispanic, no patients; black, two patients (0.2%); and Asian, no patients.

Table 2 showed that past exposure to HBV (anti-HBc–positive) with evidence for HBV recovery or immunity (anti-HBs–positive) was significantly associated with increased risk of pancreatic cancer (AOR, 2.3; $P = .01$). Past exposure to HBV without evidence of HBV recovery (anti-HBs–negative) was significantly associated with a greater risk of pancreatic cancer (AOR, 4; $P = .008$). Moreover, the effect of diabetes mellitus significantly modified the risk of pancreatic cancer among patients with past exposure to HBV; the

AOR was 7.1 (95% CI, 1.7 to 28.7) for joint history of diabetes and anti-HBc–positive. Although cases and controls were comparable in demographic factors, we chose to present the odds ratios of hepatitis virus infection after adjusting for age, sex, race, state of residency, educational level, smoking, diabetes, alcohol, and family history of cancer (Table 2).

On repeating our analysis with recoding anti-HBc of the three participants with borderline positivity as anti-HBc—negative, results did not meaningfully change. The AORs were 2.5 (95% CI, 1.4 to 4.2), 2.2 (95% CI, 1.2 to 4.3), and 4 (95% CI, 1.4 to 11.1) for overall anti-HBc–positive, anti-HBc–positive/anti-HBs–positive, and anti-HBc–positive/anti-HBs–negative, respectively.

DISCUSSION

In this study, we confirmed previously reported risk associations of pancreatic cancer with diabetes mellitus, cigarette smoking, and positive family history of cancer.[23,24,28-30] Most important, we observed an association between past exposure to HBV and risk for pancreatic cancer development.

Our finding of a relationship between chronic HBV infection and pancreatic cancer perhaps should not be surprising for two reasons. First, findings from several previous studies indicate that HBV may replicate within the pancreas. Evidence for such replication includes

Table 2. Risk Factors of Pancreatic Cancer and Association of Pancreatic Cancer With HBV or HCV Infection: Univariable and Multivariable Logistic Regression Analysis

Variable	Cases (n = 476)		Controls (n = 879)		Univariable		Multivariable	
	No.	%	No.	%	OR	95% CI	OR	95% CI
HCV								
Anti-HCV–negative	469	98.5	870	99		1 (reference)		1 (reference)
Anti-HCV–positive	7	1.5	9	1	1.4	0.5 to 3.9	0.9	0.3 to 2.8
HBV								
HBsAg-negative/Anti-HBc–negative*	440	92.4	851	96.8		1 (reference)		1 (reference)
HBsAg–positive/Anti-HBc–positive†	0	0	1	0.1		—		
HBsAg–negative/Anti-HBc–positive‡	36	7.6	27	3.1	2.5	1.5 to 4.1	2.5	1.5 to 4.2
Anti-HBc–positive/Anti-HBs–positive§	24	5	20	2.3	2.3	1.3 to 4.3	2.3	1.2 to 4.3
Anti-HBc–positive/Anti-HBs–negative¶	12	2.5	6	0.7	3.9	1.4 to 10.4	4	1.4 to 11.1
Diabetes								
No	368	77.3	792	90.1		1 (reference)		1 (reference)
Yes	108	22.7	87	9.9	2.7	1.9 to 3.6	2.9	2.1 to 4
Cigarette smoking								
No	201	42.2	451	51.3		1 (reference)		1 (reference)
Yes	275	57.8	428	48.7	1.4	1.2 to 1.8	1.4	1.1 to 1.8
Alcohol drinking								
No	198	41.6	384	43.7		1 (reference)		1 (reference)
Yes	278	58.4	495	56.3	1.1	0.9 to 1.4	1	0.8 to 1.3
Family history of cancer								
No	102	21.4	279	31.7		1 (reference)		1 (reference)
Yes	374	78.6	600	68.3	1.7	1.3 to 2.2	1.8	1.4 to 2.3

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; OR, odds ratio; anti-HBc, anti-hepatitis B core antigen; anti-HBs, anti-hepatitis B surface antigen; HBsAg, hepatitis B surface antigen.
*Never exposed.
†Chronic carrier of HBV.
‡Past exposure to HBV.
§Past exposure to HBV with natural immunity.
¶Possibly chronically infected and have an undetectable level of HBsAg present in the serum.

the following: (1) detection of HBsAg in pancreatic juice among patients with acute and chronic HBV infection.[18] This finding is analogous to detection of HBsAg in bile as a consequence of viral replication in the liver. (2) Detection of HBsAg and HBV core antigen in the cytoplasm of the acinar cells of the pancreas.[19] (3) Confirmation of HBV-DNA integration in pancreatic tissue and pancreatic metastases to the liver in patients with HBV infection.[11] (4) HBV reinfection and recurrence after liver transplantation, which may support the presence of extrahepatic reservoirs of the virus.[31-33] (5) Demonstration in animal models that HBV infection can produce hepatic diseases similar to that produced by HBV in man (eg, woodchuck HBV in woodchucks and duck HBV in Pekin duck).[34-36] Previous studies reported detection of replication-specific forms of viral nucleic acid, with evidence for duck HBsAg and duck HBV core antigen in pancreatic cells of congenitally infected Pekin ducks.[37]

The second reason why our finding of a relationship between chronic HBV infection and pancreatic cancer perhaps should not be surprising is that there have previously been clinical observations of impairment in pancreatic exocrine function in patients with chronic viral infection. Specifically, there have been reports of elevation of serum and urinary levels of pancreatic enzymes in patients with chronic HBV infection[21,22] and evidence that acute pancreatitis may be an extrahepatic manifestation or a complication of fulminant, acute, or chronic vial hepatitis.[38-41] A recent report showed that among 72 patients with acute viral hepatitis, seven patients (9.7%) developed acute pancreatitis.[42]

Interestingly, a follow-up study among Koreans[43] reported that baseline abnormal levels of liver enzymes (AST and ALT) were significantly associated with pancreatic cancer development. However, the patients' hepatitis virus infection status was not presented by the investigators.

Despite our findings and the evidence from previous studies outlined above, whether and to what extent chronic HBV infection increases the risk of pancreatic cancer is not clear. This study is the first to report an association between past exposure to HBV and pancreatic cancer. The risk was observed among patients with confirmed HBsAg-negative and anti-HBc–positive status, which suggests the possibility of occult HBV infection and long-lasting persistent viral infection. The clinical relevance of occult HBV infection is well documented.[44,45] Occult HBV infection has been described in patients negative for HBsAg who have been previously exposed to HBV and recovered from acute or chronic infection[46,47] as well as in patients with HCV infection,[48-50] patients on hemodialysis,[51] and among drug users.[52] The underlying reason for lack of detectable HBsAg in patients with occult HBV infection is unclear. However, host immune response[53,54] and HBV mutation that affect HBsAg antigenicity and synthesis[55,56] have been hypothesized. Currently, it is generally accepted that occult HBV infection among patients without any serologic evidence for HBV infection is a risk factor for HCC development.[57-59]

The mechanisms whereby HBV might induce pancreatic cancer are unclear. However, in the case of HCC, HBV-DNA integration has been detected in hepatocytes before tumor development among patients positive and negative for HBsAg, which may enhance chromosomal instability and facilitate HCC development.[60,61] In addition, the oncogenic role of the HBs and HBx proteins has been documented. HBx protein has been shown to transactivate both HBV and cellular genes, which may alter host gene expression and lead to HCC development.[62] Meanwhile, the direct necrotic and inflammatory effect

of viral hepatitis with cirrhosis cannot be excluded.[63] On reviewing the medical records of patients with pancreatic cancer with anti-HBc–positive/anti-HBs–negative status (n = 12; Table 2), we found that three patients (25%) had radiologic evidence of cirrhosis and two patients (16.7%) had pathologic evidence of chronic pancreatitis. However, our observation of the lack of association between HCV and pancreatic cancer suggests that direct inflammatory response plays a lesser role than HBV-DNA integration in pancreatic cancer development.

Another key finding of our study was the pancreatic cancer risk modification among diabetic patients with HBV infection. A high frequency of HBV and HCV infection was previously reported in diabetic patients.[64] We previously demonstrated a synergism between diabetes and hepatitis virus in the development of HCC, a disease for which HCV, HBV, and diabetes are major risk factors.[6] It is possible that the joint effect of these risk factors may increase susceptibility to chronic inflammation, DNA damage, and pancreatic cancer development.

Our study has some limitations. Because most patients with pancreatic cancer were diagnosed at a late stage, surgical tissues were not available to perform tumor HBV-DNA analysis. Moreover, we can not rule out the possibility of selection bias resulting from the use of healthy controls who were accompanying patients with cancer to the hospital; this may have overestimated or underestimated the prevalence of HBV infection among control participants. However, it is less likely that our finding of the positive relationship between HBV and pancreatic cancer is confounded by selection bias for the following reasons: (1) controls represent the study hospital from which patients with pancreatic cancer were selected[23,24]; (2) all our points of estimate were adjusted for educational level as a surrogate marker for socioeconomic status and state of residency, as well as for significant demographic and risk factors of pancreatic cancer; (3) control recruitment was restricted to individuals not having accompanying GI cancers, including HCC, a primary liver cancer that is highly related to HBV and HCV infection; (4) the prevalence of anti-HBc among our controls was consistent with the United States population prevalence of 3% (95% CI, 2.4% to 3.7%)[5]; (5) the prevalence of HBsAg among our controls was not significantly lower than the prevalence of the United States population of 0.3% (95% CI, 0.2% to 0.5%).[65] Finally, the prevalence of diabetes mellitus and other environmental risk factors were comparable to other population-based studies.[66] However, one may argue that HBV is a sexually transmitted disease, and the prevalence of HBV among our controls can be altered by sexual behavior and by the prevalence of the virus among their sexual partners. Nevertheless, the controls were not spouses of the patients with pancreatic cancer or of patients with other virus-related cancers. Moreover, the marital status of cases and controls are similar (Table 1).

In conclusion, our findings raise two crucial points. The first point is that our results indicate that past exposure and possibly chronic infection with HBV may be related to pancreatic cancer development. We found no significant association between HCV infection and pancreatic cancer. We believe that our sample size of the current matched case-control study provided more than 90% power to determine a significance relationship between past exposure to HBV infection and pancreatic cancer.[67] However, further studies, including clinicopathologic investigations, are necessary for thorough evaluation of the HBV-pancreatic cancer relationship.

The second point raised by this study is that the observed high prevalence of anti-HBc–positive status in patients with pancreatic cancer with or without anti-HBs may be an indication of an occult HBV infection. Therefore, there is a potential for reactivation of HBV among these patients when they receive chemotherapy treatment. Hepatic failure is a significant problem related to HBV reactivation in chemotherapy-treated patients with cancer.[15-17] The mechanism of HBV reactivation during chemotherapy is not clear. It has been suggested that chemotherapy may enhance the replication of HBV.[68-70] Liver failure may then develop after treatment cessation as a consequence of rebound recovery of the immune function to attack the infected liver.[71-73] Given that pancreatic cancer is often surgically unresectable, chemotherapy is the most common intervention in managing patients with pancreatic cancer. Reactivation of occult HBV infection was previously reported in a single immunosuppressed patient with pancreatic cancer.[14] However, in this study, 10 (83%) of the 12 patients with confirmed HBsAg–negative, anti-HBc–positive, anti-HBs–negative disease did not receive chemotherapy before blood was drawn and thus would not have been at risk for viral reactivation and hepatitis. Therefore, if an HBV-pancreatic cancer association is confirmed, oncologists may want to consider checking HBV status of patients before beginning chemotherapy. In addition, plasma or serum HBV-DNA may be necessary to perform among those with evidence for past exposure to HBV (anti-HBc–positive) during the course of treatment. Evidence for HBV infection among these patients should be closely monitored by hepatologists during their chemotherapy treatment. A recent report revealed a preventive role of lamivudine in persons with HBV infection who are undergoing chemotherapy.[74] Future collaboration between hepatologists and on-cologists may assist in developing guidelines for management of HBV infection among patients with cancer.

Should the association between HBV infection and pancreatic cancer be confirmed by other studies, such findings would offer an important additional insight into the etiology of pancreatic cancer and may identify a readily modifiable risk factor that can decrease the risk of pancreatic cancer.

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