Published in final edited form as:
J Clin Oncol. 2008 October 1; 26(28): 4557–4562. doi:10.1200/JCO.2008.17.3526.

Hepatitis B Virus and Pancreatic Cancer

Manal M. Hassan, **Donghui Li**, **Adel S. El-Deeb**, **Robert A. Wolff**, **Melissa L. Bondy**, **Marta Davila**, and **James L. Abbruzzese**
Departments of Gastrointestinal Medical Oncology (MMH, JLA, RAW, AED, DL), Department of Epidemiology (MB), and Department of Gastroenterology, Hepatology, and Nutrition (MD), The University of Texas M. D. Anderson Cancer Center, Houston, Texas

Abstract

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 infection increase the risk for pancreatic cancer development.

Patients and Methods—At The University of Texas M.D. Anderson Cancer Center, Houston, 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 7 cases (1.5%) and 9 controls (1%). Anti-HBc was positive in 36 cases (7.6%) and 28 controls (3.2%). The estimated AORs and 95% confidence intervals (CIs) were as follows: anti-HCV+, 0.9 (0.3–2.8), anti-HBc+, 2.5 (1.5–4.2), anti-HBc+/anti-HBs+, 2.3 (1.2–4.2), and anti-HBc+/anti-HBs-, 4 (1.4–11.1). Risk modification by past exposure to HBV was observed among diabetics (AOR, 7.1; 95% CI, 1.7–28.7).

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 on the etiology of the pancreatic cancer and may suggest the need to consider prevention of HBV reactivation among HBV-related pancreatic cancer patients during chemotherapy treatment.

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 nonliver tissue—e.g., 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

Corresponding Author: James L. Abbruzzese, Department of Gastrointestinal Medical Oncology, Unit 426, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030. Tel: (713) 792-2828; fax: (713) 745-1163; e-mail: jabbruzz@mdanderson.org.

of HBV infection in cancer patients 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]

While 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 or not 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 1144 cases and 1072 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; U.S. 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 subjects 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 subjects signed informed consent documents for participation. 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 hepatitis B surface antigen (HBsAg) and antibodies to hepatitis B core antigen (anti-HBc) and HBsAg (anti-HBs) using the enzyme-linked immunosorbent assay. The laboratory researcher running theses assays was blinded for the disease status (cases or controls) of the subjects' blood samples. Positive results prompted a repeated confirmatory

testing at 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, Texas). Blood samples were drawn from pancreatic cancer patients before chemotherapy (70%) or during follow-up visits (30%).

Three participants (2 cases and 1 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 subjects. The final status of anti-HBs was missing for one control due to 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 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 α=.05 and β= .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 to 1 control-case ratio was chosen to increase the power of the study. According to the above 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 897 controls. Thus, all 897 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 pancreatic cancer patients 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 Student's t-test was used to compare means of age between patients and controls. The chi-square 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% confidence interval (CI) using maximum likelihood estimation. The final model was chosen on the basis of biological 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 (± SD) for pancreatic patients was 60 ± 10.8 and for controls was 59. 3 ± 10.9; 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 pancreatic cancer patients (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 = <.0001.

The racial distribution of anti-HBc+ among cases was White, 31 patients (6.5%); Hispanic, 1 (0.2%); Black, 2 (0.4%); and Asian, 2 (0.4%). The racial distribution of anti-HBc+ among controls was White, 26 patients (3%); Hispanic, 0; Black, 2 (0.2%); and Asian, 0.

Table 2 showed that past exposure to HBV (anti-HBc+) with evidence for HBV recovery or immunity (anti-HBs+) 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−) 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, 1.7–28.7) for joint history of diabetes and anti-HBc+. Although cases and controls were comparable in demographic factors, we choose to present the ORs 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).

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

For two reasons our finding of a relationship between chronic HBV infection and pancreatic cancer perhaps should not be surprising. First, findings from several previous studies indicate that HBV may replicate within the pancreas. Evidence for such replication includes: 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—e.g. 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, 7 patients developed acute pancreatitis (9.7%).[42] Interestingly, a follow-up study among Koreans [43] reported that baseline abnormal levels of liver enzymes (aspirate aminotransferase and alanine aminotransferase) were significantly associated with pancreatic

cancer development. However, the subjects' 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 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 serological 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 prior to 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 trans-activate 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] Upon reviewing the medical records of pancreatic cancer patients with anti-HBc-positive/anti-HBs-negative (n=12, Table 2), we found that 3 patients (25%) had radiological evidence of cirrhosis and 2 (16.7%) had pathological 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. Due to the fact that 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 due to the use of healthy controls who were accompanying cancer patients to the hospital; which may have overestimated or underestimated the prevalence of HBV infection among control subjects. 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 pancreatic cancer patients were selected,[23, 24] 2) all our points of estimate were adjusted for educational level as a surrogate marker for socioeconomic status, state of residency as well as for significant demographic and risk factors of pancreatic cancer, 3) control recruitment was restricted to individuals not 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 USA 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 U.S. population 0.3 % (95% CI, 0.2%-0.5%).[65] Finally the prevalence of diabetes mellitus and other environmental risk factors were comparable to other population-based studies.[66] On the other side, 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 pancreatic cancer cases 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 > 90% power to determine a significance relationship between past exposure to HBV infection and pancreatic cancer.[67] However, further studies, including clinicopathological 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+ 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 upon chemotherapy treatment. Hepatic failure is a significant problem related to HBV reactivation in chemotherapy-treated cancer patients.[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 pancreatic cancer patients. Reactivation of occult HBV infection was previously reported in a single immunosuppressed pancreatic cancer patient.[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 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 +) 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 oncologists may assist in developing guidelines for management of HBV infection among cancer patients.

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

Acknowledgements

Authors would like to thank Dr. Lu-Yu Hwang at The University of Texas, School of Public Health in Houston, Texas for confirming the positive samples at her laboratory. All authors of these manuscripts contributed to the administrative functions of the study without potential competing or financial interests. Grant sponsor: Supported by National Institutes of Health (NIH) RO1 grant CA098380 (to D.L.), SPORE P20 grant CA101936 (to J.L.A.), NIEHS grant ES07784, a research grant from the Lockton Research Funds (to D.L.), NIH RO3 grant ES11481 (to M.H.),

CA106458-01 (to M.H.). All principal investigators of the above-funded studies had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Szabo E, Lotz G, Paska C, et al. Viral hepatitis: new data on hepatitis C infection. Pathol Oncol Res 2003;9:215–221. [PubMed: 14688826]
2. Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. J Viral Hepat 2004;11:97–107. [PubMed: 14996343]
3. hesa-Violante M, Nunez-Nateras R. Epidemiology of hepatitis virus B and C. Arch Med Res 2007;38:606–611. [PubMed: 17613351]
4. Rustgi VK. The epidemiology of hepatitis C infection in the United States. J Gastroenterol 2007;42:513–521. [PubMed: 17653645]
5. McQuillan GM, Kruszon-Moran D, Kottiri BJ, et al. Racial and ethnic differences in the seroprevalence of 6 infectious diseases in the United States: data from NHANES III, 1988–1994. Am J Public Health 2004;94:1952–1958. [PubMed: 15514236]
6. Hassan MM, Hwang LY, Hatten CJ, et al. Risk factors for hepatocellular carcinoma: synergism of alcohol with viral hepatitis and diabetes mellitus. Hepatology 2002;36:1206–1213. [PubMed: 12395331]
7. Welzel TM, Graubard BI, El-Serag HB, et al. Risk factors for intrahepatic and extrahepatic cholangiocarcinoma in the United States: a population-based case-control study. Clin Gastroenterol Hepatol 2007;5:1221–1228. [PubMed: 17689296]
8. Shaib YH, El-Serag HB, Nooka AK, et al. Risk factors for intrahepatic and extrahepatic cholangiocarcinoma: a hospital-based case-control study. Am J Gastroenterol 2007;102:1016–1021. [PubMed: 17324130]
9. Nowoslawski A, Krawczynski K, Brzosko WJ, et al. Tissue localization of Australia antigen immune complexes in acute and chronic hepatitis and liver cirrhosis. Am J Pathol 1972;68:31–56. [PubMed: 4628111]
10. Trepo CG, Zucherman AJ, Bird RC, et al. The role of circulating hepatitis B antigen/antibody immune complexes in the pathogenesis of vascular and hepatic manifestations in polyarteritis nodosa. J Clin Pathol 1974;27:863–868. [PubMed: 4155412]
11. Dejean A, Lugassy C, Zafrani S, et al. Detection of hepatitis B virus DNA in pancreas, kidney and skin of two human carriers of the virus. J Gen Virol 1984;65 (Pt 3):651–655. [PubMed: 6699625]
12. Ulcickas YM, Quesenberry CP Jr, Guo D, et al. Incidence of non-Hodgkin's lymphoma among individuals with chronic hepatitis B virus infection. Hepatology 2007;46:107–112. [PubMed: 17526021]
13. Dal ML, Franceschi S. Hepatitis C virus and risk of lymphoma and other lymphoid neoplasms: a meta-analysis of epidemiologic studies. Cancer Epidemiol Biomarkers Prev 2006;15:2078–2085. [PubMed: 17119031]
14. Oksuzoglu B, Kilickap S, Yalcin S. Reactivation of hepatitis B virus infection in pancreatic cancer: a case report. Jpn J Clin Oncol 2002;32:543–545. [PubMed: 12578904]
15. Pinto PC, Hu E, Bernstein-Singer M, et al. Acute hepatic injury after the withdrawal of immunosuppressive chemotherapy in patients with hepatitis B. Cancer 1990;65:878–884. [PubMed: 2297658]
16. Soh LT, Ang PT, Sng I, et al. Fulminant hepatic failure in non-Hodgkin lymphoma patients treated with chemotherapy. Eur J Cancer 1992;28A:1338–1339. [PubMed: 1381211]
17. Thung SN, Gerber MA, Klion F, et al. Massive hepatic necrosis after chemotherapy withdrawal in a hepatitis B virus carrier. Arch Intern Med 1985;145:1313–1314. [PubMed: 4015284]
18. Hoefs JC, Renner IG, Askhcavai M, et al. Hepatitis B surface antigen in pancreatic and biliary secretions. Gastroenterology 1980;79:191–194. [PubMed: 7399225]
19. Yoshimura M, Sakurai I, Shimoda T, et al. Detection of HBsAg in the pancreas. Acta Pathol Jpn 1981;31:711–717. [PubMed: 7025575]

20. Shimoda T, Shikata T, Karasawa T, et al. Light microscopic localization of hepatitis B virus antigens in the human pancreas. Possibility of multiplication of hepatitis B virus in the human pancreas. Gastroenterology 1981;81:998–1005. [PubMed: 6169587]
21. Taranto D, Carrato A, Romano M, et al. Mild pancreatic damage in acute viral hepatitis. Digestion 1989;42:93–97. [PubMed: 2475380]
22. Katakura Y, Yotsuyanagi H, Hashizume K, et al. Pancreatic involvement in chronic viral hepatitis. World J Gastroenterol 2005;11:3508–3513. [PubMed: 15962364]
23. Hassan MM, Abbruzzese JL, Bondy ML, et al. Passive smoking and the use of noncigarette tobacco products in association with risk for pancreatic cancer: a case-control study. Cancer 2007;109:2547–2556. [PubMed: 17492688]
24. Hassan MM, Bondy ML, Wolff RA, et al. Risk Factors for Pancreatic Cancer: Case-Control Study. Am J Gastroenterol. 2007
25. Lok AS, McMahon BJ. Chronic hepatitis B. Hepatology 2007;45:507–539. [PubMed: 17256718]
26. Lee WM. Hepatitis B virus infection. N Engl J Med 1997;337:1733–1745. [PubMed: 9392700]
27. Pawlotsky JM, Lonjon I, Hezode C, et al. What strategy should be used for diagnosis of hepatitis C virus infection in clinical laboratories? Hepatology 1998;27:1700–1702. [PubMed: 9620345]
28. Silverman DT, Dunn JA, Hoover RN, et al. Cigarette smoking and pancreas cancer: a case-control study based on direct interviews. J Natl Cancer Inst 1994;86:1510–1516. [PubMed: 7932805]
29. Silverman DT, Schiffman M, Everhart J, et al. Diabetes mellitus, other medical conditions and familial history of cancer as risk factors for pancreatic cancer. Br J Cancer 1999;80:1830–1837. [PubMed: 10468306]
30. Everhart J, Wright D. Diabetes mellitus as a risk factor for pancreatic cancer. A meta-analysis JAMA 1995;273:1605–1609.
31. Olivera-Martinez MA, Gallegos-Orozco JF. Recurrent viral liver disease (hepatitis B and C) after liver transplantation. Arch Med Res 2007;38:691–701. [PubMed: 17613360]
32. Polak WG, Gladysz A, Rotter K. Prevention of hepatitis B recurrence after liver transplantation. Ann Transplant 2005;10:11–16. [PubMed: 16617660]
33. Montalbano M, Neff GW. Management of recurrent viral hepatitis B and C after liver transplantation. Curr Gastroenterol Rep 2006;8:60–66. [PubMed: 16510036]
34. Jilbert AR, Freiman JS, Gowans EJ, et al. Duck hepatitis B virus DNA in liver, spleen, and pancreas: analysis by in situ and Southern blot hybridization. Virology 1987;158:330–338. [PubMed: 3590623]
35. Halpern MS, Egan J, McMahon SB, et al. Duck hepatitis B virus is tropic for exocrine cells of the pancreas. Virology 1985;146:157–161. [PubMed: 3898564]
36. Ogston CW, Schechter EM, Humes CA, et al. Extrahepatic replication of woodchuck hepatitis virus in chronic infection. Virology 1989;169:9–14. [PubMed: 2922930]
37. Halpern MS, England JM, Deery DT, et al. Viral nucleic acid synthesis and antigen accumulation in pancreas and kidney of Pekin ducks infected with duck hepatitis B virus. Proc Natl Acad Sci U S A 1983;80:4865–4869. [PubMed: 6576362]
38. Parbhoo SP, Welch J, Sherlock S. Acute pancreatitis in patients with fulminant hepatic failure. Gut 1973;14:428. [PubMed: 4716531]
39. de Oliveira LC, Rezende PB, Ferreira AL, et al. Concurrent acute hepatitis and pancreatitis associated with hepatitis B virus: case report. Pancreas 1998;16:559–561. [PubMed: 9598823]
40. Yuen MF, Chan TM, Hui CK, et al. Acute pancreatitis complicating acute exacerbation of chronic hepatitis B infection carries a poor prognosis. J Viral Hepat 2001;8:459–464. [PubMed: 11703578]
41. Mishra A, Saigal S, Gupta R, et al. Acute pancreatitis associated with viral hepatitis: a report of six cases with review of literature. Am J Gastroenterol 1999;94:2292–2295. [PubMed: 10445566]
42. Jain P, Nijhawan S. Acute viral hepatitis with pancreatitis: is it due to the viruses or sludge? Pancreatology 2007;7:544–545. [PubMed: 17901717]
43. Berrington de GA, Yun JE, Lee SY, et al. Pancreatic cancer and factors associated with the insulin resistance syndrome in the korean cancer prevention study. Cancer Epidemiol Biomarkers Prev 2008;17:359–364. [PubMed: 18268120]
44. Munoz SJ. Use of hepatitis B core antibody-positive donors for liver transplantation. Liver Transpl 2002;8:S82–S87. [PubMed: 12362304]

45. Fukuda R, Ishimura N, Niigaki M, et al. Serologically silent hepatitis B virus coinfection in patients with hepatitis C virus-associated chronic liver disease: clinical and virological significance. J Med Virol 1999;58:201–207. [PubMed: 10447413]
46. Tamori A, Nishiguchi S, Kubo S, et al. HBV DNA integration and HBV-transcript expression in non-B, non-C hepatocellular carcinoma in Japan. J Med Virol 2003;71:492–498. [PubMed: 14556260]
47. Kannangai R, Molmenti E, Arrazola L, et al. Occult hepatitis B viral DNA in liver carcinomas from a region with a low prevalence of chronic hepatitis B infection. J Viral Hepat 2004;11:297–301. [PubMed: 15230851]
48. Cacciola I, Pollicino T, Squadrito G, et al. Occult hepatitis B virus infection in patients with chronic hepatitis C liver disease. N Engl J Med 1999;341:22–26. [PubMed: 10387938]
49. Kao JH, Chen PJ, Lai MY, et al. Occult hepatitis B virus infection and clinical outcomes of patients with chronic hepatitis C. J Clin Microbiol 2002;40:4068–4071. [PubMed: 12409376]
50. Georgiadou SP, Zachou K, Rigopoulou E, et al. Occult hepatitis B virus infection in Greek patients with chronic hepatitis C and in patients with diverse nonviral hepatic diseases. J Viral Hepat 2004;11:358–365. [PubMed: 15230859]
51. Besisik F, Karaca C, Akyuz F, et al. Occult HBV infection and YMDD variants in hemodialysis patients with chronic HCV infection. J Hepatol 2003;38:506–510. [PubMed: 12663244]
52. Lin CL, Liu CJ, Chen PJ, et al. High prevalence of occult hepatitis B virus infection in Taiwanese intravenous drug users. J Med Virol 2007;79:1674–1678. [PubMed: 17854041]
53. Lok AS, Liang RH, Chiu EK, et al. Reactivation of hepatitis B virus replication in patients receiving cytotoxic therapy. Report of a prospective study. Gastroenterology 1991;100:182–188. [PubMed: 1983820]
54. Guidotti LG, Chisari FV. Noncytolytic control of viral infections by the innate and adaptive immune response. Annu Rev Immunol 2001;19:65–91. [PubMed: 11244031]
55. Hou J, Karayiannis P, Waters J, et al. A unique insertion in the S gene of surface antigen--negative hepatitis B virus Chinese carriers. Hepatology 1995;21:273–278. [PubMed: 7843693]
56. Chaudhuri V, Tayal R, Nayak B, et al. Occult hepatitis B virus infection in chronic liver disease: full-length genome and analysis of mutant surface promoter. Gastroenterology 2004;127:1356–1371. [PubMed: 15521005]
57. Paterlini P, Gerken G, Nakajima E, et al. Polymerase chain reaction to detect hepatitis B virus DNA and RNA sequences in primary liver cancers from patients negative for hepatitis B surface antigen. N Engl J Med 1990;323:80–85. [PubMed: 2359427]
58. Paterlini P, Driss F, Nalpas B, et al. Persistence of hepatitis B and hepatitis C viral genomes in primary liver cancers from HBsAg-negative patients: a study of a low-endemic area. Hepatology 1993;17:20–29. [PubMed: 8380790]
59. Sheu JC, Huang GT, Shih LN, et al. Hepatitis C and B viruses in hepatitis B surface antigen-negative hepatocellular carcinoma. Gastroenterology 1992;103:1322–1327. [PubMed: 1327934]
60. Brechot C. Hepatitis B virus (HBV) and hepatocellular carcinoma. HBV DNA status and its implications. J Hepatol 1987;4:269–279. [PubMed: 3035005]
61. Brechot C, Pourcel C, Louise A, et al. Presence of integrated hepatitis B virus DNA sequences in cellular DNA of human hepatocellular carcinoma. Nature 1980;286:533–535. [PubMed: 6250074]
62. Rossner MT. Review: hepatitis B virus X-gene product: a promiscuous transcriptional activator. J Med Virol 1992;36:101–117. [PubMed: 1583465]
63. Simonetti RG, Camma C, Fiorello F, et al. Hepatitis C virus infection as a risk factor for hepatocellular carcinoma in patients with cirrhosis. A case-control study. Ann Intern Med 1992;116:97–102. [PubMed: 1309286]
64. Sangiorgio L, Attardo T, Gangemi R, et al. Increased frequency of HCV and HBV infection in type 2 diabetic patients. Diabetes Res Clin Pract 2000;48:147–151. [PubMed: 10802152]
65. McQuillan GM, Coleman PJ, Kruszon-Moran D, et al. Prevalence of hepatitis B virus infection in the United States: the National Health and Nutrition Examination Surveys, 1976 through 1994. Am J Public Health 1999;89:14–18. [PubMed: 9987458]
66. Wang F, Gupta S, Holly EA. Diabetes mellitus and pancreatic cancer in a population-based case-control study in the San Francisco Bay Area, California. Cancer Epidemiol Biomarkers Prev 2006;15:1458–1463. [PubMed: 16896032]

67. Schlesselman JJ. Sample size requirements in cohort and case-control studies of disease. Am J Epidemiol 1974;99:381–384. [PubMed: 4601871]

68. Cheng AL. Steroid-free chemotherapy decreases the risk of hepatitis flare-up in hepatitis B virus carriers with non-Hodgkin's lymphoma. Blood 1996;87:1202. [PubMed: 8562950]

69. Chou CK, Wang LH, Lin HM, et al. Glucocorticoid stimulates hepatitis B viral gene expression in cultured human hepatoma cells. Hepatology 1992;16:13–18. [PubMed: 1319949]

70. Scullard GH, Smith CI, Merigan TC, et al. Effects of immunosuppressive therapy on viral markers in chronic active hepatitis B. Gastroenterology 1981;81:987–991. [PubMed: 7286593]

71. Alexander GJ, Nouri-Aria KT, Eddleston AL, et al. Contrasting relations between suppressor-cell function and suppressor-cell number in chronic liver disease. Lancet 1983;1:1291–1293. [PubMed: 6134091]

72. Hanson RG, Peters MG, Hoofnagle JH. Effects of immunosuppressive therapy with prednisolone on B and T lymphocyte function in patients with chronic type B hepatitis. Hepatology 1986;6:173–179. [PubMed: 2937707]

73. Mondelli M, Vergani GM, Alberti A, et al. Specificity of T lymphocyte cytotoxicity to autologous hepatocytes in chronic hepatitis B virus infection: evidence that T cells are directed against HBV core antigen expressed on hepatocytes. J Immunol 1982;129:2773–2778. [PubMed: 6982941]

74. Loomba R, Rowley A, Wesley R, et al. Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy. Ann Intern Med 2008;148:519–528. [PubMed: 18378948]

Table 1

Characteristics of study population

Variable	Cases N = 476 (%)	Controls N= 879 (%)	P value
Age (years)			.4
≤50	100 (21)	194 (22.1)	
> 50	376 (79)	685 (77.9)	
Race			.1
Whites	437 (91.8)	769 (87.5)	
Hispanics	20 (4.2)	68 (7.7)	
Blacks	14 (2.9)	35 (4)	
Sex			.4
Females	177 (37.2)	347 (39.5)	
Males	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 USA 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, New Mexico

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 OR (95% CI)	Multivariable OR (95% CI)
HCV				
Anti-HCV −	469 (98.5)	870 (99)	1 (reference)	
Anti-HCV +	7 (1.5)	9 (1)	1.4 (.5–3.9)	.9 (.3–2.8)
HBV				
HBsAg-/Anti-HBc− *	438 (92)	844 (96)	1 (reference)	
HBsAg+/Anti-HBc+ †	0	1 (.1)	————	
HBsAg−/Anti-HBc + ‡	36 (7.6)	27 (3.1)	2.5 (1.5–4.1)	2.5 (1.5–4.2)
Anti-HBc+/Anti-HBs+§	24 (5)	20 (2.3)	2.3 (1.3–4.3)	2.3 (1.2–4.3)
Anti-HBc+/Anti-HBs− ¶	12 (2.5)	6 (.7)	3.9 (1.4–10.4)	4 (1.4–11.1)
Diabetes				
No	368 (77.3)	792 (90.1)	1 (reference)	
Yes	108 (23.7)	87 (9.9)	2.7 (1.9–3.6)	2.9 (2.1–4)
Cigarette smoking				
No	201 (42.2)	451 (51.3)	1 (reference)	
Yes	275 (57.8)	428 (48.7)	1.4 (1.2–1.8)	1.4 (1.1–1.8)
Alcohol drinking				
No	198 (41.6)	384 (43.7)	1 (reference)	
Yes	278 (58.8)	495 (56.3)	1.1 (.9–1.4)	1 (.8–1.3)
Family history of cancer				
No	102 (21.4)	279 (31.7)	1 (reference)	
Yes	374 (78.6)	600 (68.3)	1.7 (1.3–2.2)	1.8 (1.4–2.3)

Abbreviations: +, positive; −, negative; anti-HBc, anti-hepatitis B core antigen; anti-HBs, anti-hepatitis B surface antigen; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.

* Never exposed;

† Chronic carrier of HBV;

‡ Past exposure to HBV;

§ Past exposure to HBV with natural immunity;

¶ Possible chronically infected and have an undetectable level of HBsAg present in the serum.