

No Association Between Hepatitis B and Pancreatic Cancer in a Prospective Study in Korea

TO THE EDITOR: We read with interest the report of a finding of an association between hepatitis B infection and the risk of pancreatic cancer in a large-scale case-control study by Hassan et al.¹ They reported a two- to three-fold increased risk of pancreatic cancer in those who tested positive for hepatitis B core antibody (anti-HBc). The authors suggested this was the first study to investigate an association between this virus and pancreatic cancer. However, we published the results of a large prospective cohort study of Koreans, which suggested no association between pancreatic cancer and hepatitis B.²

In the Korean study, 664 patients were diagnosed with pancreatic cancer after a median follow-up of 12 years, in a study population of 201,975 individuals with test results for hepatitis B surface antigen (HBsAg) status. Chronic hepatitis B is endemic in Korea, and overall, 8% of the study population tested positive for HBsAg. This figure was similar among the patients with pancreatic cancer, resulting in an adjusted relative risk for HBsAg positivity of 1.13 (95% CI, 0.84 to 1.52). The cohort consisted of Koreans insured by the National Health Insurance Corp, and the HBsAg results were from a routine medical examination of the insured workers conducted at study entry. Their dependents were not required to undergo this medical examination, which is why test results were only available for 32% of the total study population of 631,172.

In the study by Hassan et al,¹ none of the patients, and only one individual in the control group, tested HBsAg positive. The reported association with pancreatic cancer pertained to anti-HBc rather than to HBsAg positivity. They found a positive association in patients testing anti-HBc positive/HBsAg positive, which indicates resolved infection,³ and also in patients testing anti-HBc positive/HBsAg negative, which may indicate occult hepatitis B infection. Occult hepatitis B viral infection occurs when chronically infected individuals do not have detectable circulating HBsAg. However, in some individuals, isolated anti-HBc positivity may indicate a false-positive test result (ie, these individuals may never have been infected).⁴ Although the serologic pattern reported by Hassan et al suggests occult infection, formal diagnosis relies on demonstration of hepatitis DNA in serum or liver tissue,⁵ which was not investigated.

HBsAg is a sensitive marker for chronic hepatitis B infection,³ and it is these chronic infections, rather than resolved or occult infec-

tions, that are associated with a high risk of developing hepatocellular cancer.⁶ In a previous study in this Korean cohort, a strong association between HBsAg and hepatocellular carcinoma was seen,⁶ and the magnitude of increased risk was similar to that reported in prior studies.⁷ It is not clear from a biologic viewpoint why resolved or occult hepatitis B viral infection would be associated with elevated pancreatic cancer risk, as suggested by the findings of Hassan et al, when readily detectable chronic infection is not. Because of these uncertainties, the potential association between hepatitis B viral infection and pancreatic cancer, although interesting, should currently be interpreted with caution. Evaluation of pancreatic cancer specimens for the presence of hepatitis B DNA would be a useful next step.

Amy Berrington de Gonzalez

Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD

Sun-Ha Jee

Department of Epidemiology and Health Promotion, Yonsei University, Korea

Eric A. Engels

Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

REFERENCES

- Hassan MM, Li D, El-Deeb AS, et al: Association between hepatitis B virus and pancreatic cancer. *J Clin Oncol* 26:4557-4562, 2008
- Berrington de Gonzalez A, 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* 17:359-364, 2008
- Koziel MJ, Saddiqui A: Hepatitis B virus and hepatitis delta virus, in Mandell GL, Bennett JE, Dolin R (eds): *Principles and Practice of Infectious Diseases* (ed 6). Philadelphia, PA, Elsevier, 2005, pp 1864-1890
- Raimondo G, Pollicino T, Cacciola I, et al: Occult hepatitis B virus infection. *J Hepatol* 46:160-170, 2007
- Lok AS, McMahon BJ: Chronic hepatitis B. *Hepatology* 45:507-539, 2007
- International Agency for Research on Cancer: *Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol 59: Hepatitis B Virus*. Lyon, France, International Agency for Research on Cancer, 1994
- Jee SH, Ohrr H, Sull JW, et al: Cigarette smoking, alcohol drinking, hepatitis B, and risk for hepatocellular carcinoma in Korea. *J Natl Cancer Inst* 96:1851-1856, 2004

DOI: 10.1200/JCO.2008.20.7514; published online ahead of print at www.jco.org on December 22, 2008

IN REPLY: We appreciate the thoughtful comments of Berrington de Gonzalez et al, who make two points related to our recently published article.¹ First, they state, "The authors suggested that this was the first study to investigate an association between this [hepatitis B] virus and pancreatic cancer." In our report, we acknowledged the work by Berrington de Gonzalez et al related to the association between elevated liver enzymes and pancreatic cancer (cited as reference 43). However, we did not comment on the authors' report of a nonsignificant association between hepatitis B virus (HBV) surface antigen (HBsAg) and pancreatic cancer, because we believed that the analysis of this association was a post-hoc analysis, and the study was not designed to address the association between HBV infection and

pancreatic cancer. Our reasons for this belief were, first, pancreatic cancer was diagnosed according to the International Statistical Classification of Diseases and Related Health Problems (C25, 10th revision; WHO); thus, the study included patients with all types of pancreatic neoplasms, including neuroendocrine and unspecified pancreatic tumors, rather than just patients with pancreatic adenocarcinoma. Second, patients with underlying liver diseases were excluded; thus, there was no information about the viral status of these patients, nor about the incidence of pancreatic cancer among these patients. Third, data on HBsAg were missing for 68% of the study population. Fourth, no information was provided regarding the laboratory methodology used for HBsAg testing, or whether the HBsAg-positive results were