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Philip R. Spradling

Jian Xing

Y Zhong

Loralee B. Rupp
Henry Ford Health, lrupp1@hfhs.org

Anne C. Moorman

See next page for additional authors

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Authors

Philip R. Spradling, Jian Xing, Y Zhong, Loralee B. Rupp, Anne C. Moorman, Mei Lu, Eyasu H. Teshale, Mark A. Schmidt, Yihe G. Daida, Joseph A. Boscarino, and Stuart C. Gordon

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BRIEF REPORT

Incidence of Malignancies Among Patients With Chronic Hepatitis B in US Health Care Organizations, 2006–2018

Philip R. Spradling,[1] Jian Xing,[1] Yuna Zhong,[1] Loralee B. Rupp,[2] Anne C. Moorman,[1] Mei Lu,[2] Eyasu H. Teshale,[1] Mark A. Schmidt,[3] Yihe G. Daida,[4] Joseph A. Boscarino,[5] and Stuart C. Gordon[2,6]; for the Chronic Hepatitis Cohort Study Investigators

[1]Division of Viral Hepatitis, Centers for Disease Control and Prevention, Atlanta, Georgia, USA, [2]Henry Ford Health System, Detroit, Michigan, USA, [3]The Center for Health Research, Kaiser Permanente Northwest, Portland, Oregon, USA, [4]The Center for Integrated Health Care Research, Kaiser Permanente Hawaii, Honolulu, Hawaii, USA, [5]Department of Population Health Sciences, Geisinger Clinic, Danville, Pennsylvania, USA, and [6]Wayne State University School of Medicine, Detroit, Michigan, USA

Hepatitis B virus (HBV) infection causes hepatocellular carcinoma but its association with other cancers is not well established. We compared age-adjusted incidence of primary cancers among 5773 HBV-infected persons with US cancer registries during 2006–2018. Compared with the US population, substantially higher incidence among HBV-infected persons was observed for hepatocellular carcinoma (standardized rate ratio [SRR], 30.79), gastric (SRR, 7.95), neuroendocrine (SRR, 5.88), cholangiocarcinoma (SRR, 4.62), and ovarian (SRR, 3.72) cancers, and non-Hodgkin lymphoma (SRR, 2.52). Clinicians should be aware of a heightened potential for certain nonhepatic malignancies among hepatitis B patients, as earlier diagnosis favors improved survival.

Keywords. cancer; hepatitis B; incidence.

Hepatitis B virus (HBV) infection causes hepatocellular carcinoma (HCC); however, findings from studies examining its association with nonliver cancers have been largely inconsistent [1–3]. HBV DNA has been identified in nonhepatic sites, including the pancreas, stomach, biliary tract, kidney, lymphatic tissue, ovary, and peripheral mononuclear cells [3–5]. In hepatocytes, integration of HBV DNA into the host genome induces the expression of cancer-related genes, and immune-mediated chronic inflammation and regeneration are believed to augment the accumulation of mutations that result in malignancy [6]. Plausible oncogenic processes for nonhepatic sites, however, have not been thoroughly elucidated. For clinicians, awareness of a heightened potential for certain nonhepatic malignancies among hepatitis B patients could prompt an expeditious assessment of potentially relevant signs and symptoms, leading to earlier diagnosis. Most studies examining cancers among HBV-infected persons have been conducted in Asia, while those in the United States have been limited to selected populations or cancers [1, 7]. Our objective, therefore, was to compare the incidence of various cancers among patients with chronic HBV infection with that of the general US population.

METHODS

Study Population

We analyzed data from patients with chronic HBV infection who received health care services at all 4 Chronic Hepatitis Cohort Study (CHeCS) sites: Geisinger Health System (Danville, Pennsylvania), Henry Ford Health System (Detroit, Michigan), Kaiser Permanente-Northwest (Portland, Oregon), and Kaiser Permanente Hawaii (Honolulu). The cohort was created based on analysis of electronic health records and administrative data (supplemented with individual chart review) of approximately 2.7 million adults with ≥ 1 clinical service visit beginning 1 January 2006. Patients who met a combination of laboratory-based and International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)-based criteria consistent with chronic HBV infection were included, as previously described [8]. Once patients met cohort inclusion criteria, all retrospective data were incorporated into the database. Prospective data were available through 31 December 2018, which included patient demographics, medical encounters, tumor registry data, and laboratory results. Hepatitis B patients with (previous or current) hepatitis C virus or human immunodeficiency virus coinfection were excluded from this analysis. The study protocol was reviewed and approved by an institutional review board annually at each study site. The CHeCS investigation follows the guidelines of the US Department of Health and Human Services regarding the protection of human subjects.

Identification of Incident Primary Cancers in the Hepatitis B Cohort and National Tumor Registries

For the hepatitis B cohort, tumor registry data were collected according to Surveillance, Epidemiology, and End Results (SEER) program standards [9]. Using tumor registry data, we identified primary cancers diagnosed among HBV-infected patients during 2006–2018, according to International Classification of Disease for Oncology, third edition (ICD-O-3) classification, by anatomic site, morphological, and behavioral codes. Among

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Correspondence: Philip R. Spradling, MD, Division of Viral Hepatitis, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, MS US12-3, 1600 Clifton Road NE, Atlanta, GA (pspradling@cdc.gov).

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incident neoplasms whose malignant status was not discernible directly from the morphological code, we used the behavioral code to confirm malignancy (eg, to differentiate adenomas from adenocarcinomas). All recurrent cancers were excluded from the analysis, as were primary cancers diagnosed before 1 January 2006. We subsequently excluded uncommon cancers from incidence calculations (ie, < 5 cases during the 12-year study period).

To identify incident primary cancers in the US population, we used 2 registry data sources: (1) SEER 18, from the National Cancer Institute, provided cancer incidence and survival data from 18 US states and metropolitan area registries [9]; and (2) National Program of Cancer Registries (NPCR), administered by the US Centers for Disease Control and Prevention [10]. Together, these complimentary registries represented 97% of the US population. After identification of incident cancers among hepatitis B patients, each with an ICD-0-3 site, morphological, and behavioral code, we used these same codes to identify identical incident cancers in the general population using SEER and NCPR (Supplementary Table). Cancers were ultimately classified and compared according to anatomic site, except for hematologic malignancies, lymphomas, and neuroendocrine (NE) cancers.

Statistical Analyses and Comparison of Incident Primary Cancers in the Hepatitis B Cohort Versus US Population

Incidence was calculated for persons aged ≥ 20 years as the number of newly diagnosed malignant cancer cases in the hepatitis B cohort and in SEER/NPCR from 1 January 2006 to 31 December 2018. Incidence was expressed per 100 000 prospective person-years of observation. Person-years were calculated for the hepatitis B cohort from first observation to cancer diagnosis, last date of follow-up, or death. Primary cancers diagnosed before the first encounter in the study-affiliated health care system were considered prevalent and excluded from the analysis. For comparison, cancer incidence rates for the hepatitis B cohort and for the US population were age-adjusted by directly standardizing to the 2012 US Census population estimate. Standardized rate ratios (SRR) were determined for the entire observation period to compare cancer incidence in the hepatitis B cohort with that of the general population. Statistical analyses were performed using SEER/Stat software version 8.1.2 (Surveillance Research Program, National Cancer Institute, seer.cancer.gov/seerstat), and with SAS software version 9.2 (SAS Institute).

RESULTS

There were 5773 HBV-infected patients in the hepatitis B cohort during the study period, contributing 35 250 person-years of follow-up; the mean follow-up was 6.3 years, 53.0% of patients were male, 66.2% were aged 30–60 years at entry, 47.7% were of Asian/Pacific Islander descent, and 63.8% were privately insured.

There were 385 incident primary cancers among 349 hepatitis B patients during 2006–2018. Table 1 shows rates with 95% confidence intervals (CI) for 283 cancers among 269 patients for which incidence was determined (≥5 incident cases during 2006–2018). Compared with the general population, incidence was substantially higher among hepatitis B patients for the following cancers: HCC (SRR, 30.79), gastric (SRR, 7.95), NE (SRR, 5.88), cholangiocarcinoma (SRR, 4.62), ovarian (SRR, 3.72), and non-Hodgkin lymphoma (NHL) (SRR, 2.52). Differences in incidence were less pronounced for renal (SRR, 1.87), colorectal (SRR, 1.50), breast (SRR, 1.46), pancreatic (SRR, 1.36), thyroid (SRR, 1.31), and lung/bronchus (SRR, 1.17) cancers. The 15 incident NHL cases in the hepatitis B cohort included: diffuse large B-cell lymphoma (DLBCL) (n = 4); chronic lymphocytic leukemia (n = 3); marginal zone B-cell (n = 2); T-cell (n = 2); non-Hodgkin lymphoma, not otherwise specified (n = 2); follicular (n = 1); and mantle cell (n = 1). The 7 incident NE cancers included 5 carcinoid (ICD-O-3 morphological code 8240) and 2 NE (morphological code 8246) tumors; all 7 were malignant (ie, ICD-O-3 behavioral code 3). These occurred in the lung (n = 2), pancreas (n = 2), colon (n = 2), and small intestine (n = 1), and were diagnosed at all 4 study sites; 5 cases were female and 5 were of Asian/Pacific Island descent; all were aged 55–75 years at diagnosis.

In contrast, the incidence of bladder (SRR, 0.84) and prostate (SRR, 0.64) cancers among hepatitis B patients was lower than in the general population.

DISCUSSION

In this cohort of 5773 HBV-infected patients we found that the incidence of several malignancies substantially exceeded those of the US population: these included HCC, NE, gastric, cholangiocarcinoma, ovarian, and NHL. Numerous studies examining various populations, using assorted methodological approaches, have resulted in a lengthy list of nonhepatic cancers potentially associated with HBV infection. Our findings of elevated rates of HCC, gastric cancer, cholangiocarcinoma, and NHL are consistent with those of most investigators. In contrast, none to our knowledge have reported an increased rate of ovarian cancer among persons with chronic hepatitis B (although replicative HBV has been detected in ovarian tissue) [5, 11, 12]. Several investigators have found an epidemiologic association of HBV with pancreatic cancer, and HBV has been detected in pancreatic tissue [12, 13]. However, we found only a modestly increased rate of pancreatic cancer in our hepatitis B cohort compared with the US population.

As a homogeneous entity, NHL frequently has been associated with HBV infection [2, 3, 11, 12]. Classified accordingly, we too found a significantly elevated rate of NHL in the study

Table 1. Comparison of Primary Cancer Incidence Among Patients With Hepatitis B in the Chronic Hepatitis Cohort Study (CHeCS) Versus the US Population, According to the National Program of Cancer Registries (NPCR) and Surveillance, Epidemiology and End Results Program (SEER) Cancer Registries, 2006–2018

Cancers	CHeCS Cancers, n (Column %), n = 283[a]	CHeCS Standardized Age-Adjusted Incidence (95% CI)[b]	NNCPR/SEER[c] Standardized Age-Adjusted Incidence (95% CI)[b]	Standardized Rate Ratio (95% CI)[h]
Hepatocellular carcinoma	98 (34.6)	304.5 (242.5–379.9)	9.9 (9.8–10.0)	30.79 (30.38–31.20)
Gastric	5 (1.8)	16.1 (4.7–43.8)	2.0 (2.0–2.0)	7.95 (7.71–8.20)
Neuroendocrine[d]	7 (2.5)	23.1 (8.4–53.9)	3.9 (3.9–4.0)	5.88 (5.75–6.01)
Cholangiocarcinoma	7 (2.5)	20.1 (7.5–48.3)	4.4 (4.3–4.4)	4.62 (4.52–4.72)
Ovarian[e]	5 (1.8)	29.9 (9.7–92.8)	8.0 (8.0–8.1)	3.72 (3.64–3.81)
Non-Hodgkin lymphoma[f]	15 (5.3)	43.3 (23.1–77.8)	17.2 (17.1–17.3)	2.52 (2.49–2.55)
Renal	13 (4.6)	40.1 (20.5–74.5)	22.0 (21.9–22.1)	1.87 (1.85–1.89)
Colorectal	23 (8.1)	77.7 (47.5–122.7)	51.5 (51.3–51.6)	1.50 (1.49–1.51)
Breast[e]	36 (12.7)	233.4 (156.5–346.2)	159.8 (159.4–160.2)	1.46 (1.45–1.47)
Pancreas	9 (3.2)	21.8 (9.9–48.0)	16.0 (15.9–16.1)	1.36 (1.34–1.38)
Thyroid	7 (2.5)	22.0 (8.3–51.1)	16.8 (16.7–17.0)	1.31 (1.29–1.32)
Lung/bronchus	32 (11.3)	105.8 (69.7–156.3)	90.4 (90.2–90.6)	1.17 (1.16–1.18)
Bladder	5 (1.8)	17.9 (5.1–47.8)	21.4 (21.4–21.5)	0.84 (.82–.85)
Prostate[g]	21 (7.4)	115.0 (67.4–185.6)	180.7 (180.3–181.1)	0.64 (.63–.64)

[a]In total, 283 selected cancer cases (where n ≥ 5) among 269 chronic hepatitis B patients; 14 second incident cancers were histologically distinct from the first.

[b]Per 100 000 prospective person-years of observation. Based on US Census Bureau 2012 data with age groups: 20–49, 50–59, 60–69, and 70 years and older.

[c]NPCR and SEER Incidence—US Cancer Statistics Public Use Database, 2020 submission (2001–2018) [10].

[d]The 7 incident malignant (ie, ICD-O-3 behavioral code 3) carcinoid (morphological code 8240; n = 5) or neuroendocrine (morphological code 8246; n = 2) cancers occurred in the pancreas (n = 2), colon (n = 2), lung (n = 2), and small intestine (n = 1).

[e]Female only

[f]Includes large B-cell, diffuse (n = 4); chronic lymphocytic leukemia (n = 3); marginal zone B-cell (n = 2); T-cell (n = 2); non-Hodgkin lymphoma, not otherwise specified (n = 2); follicular (n = 1); and mantle cell (n = 1).

[g]Male only.

[h]Standardized rate ratios are displayed to 2 decimal places to distinguish point estimates from confidence intervals.

cohort. However, the 15 incident NHL cases in our cohort comprised 7 different cell types, none of which had more than 4 incident cases during study follow-up, and thus would have been removed per exclusion criteria from this analysis if classified separately. In a study of Medicare recipients by investigators at the US National Cancer Institute, HBV infection was positively associated with DLBCL (also the most common NHL in our study cohort) but negatively associated with chronic lymphocytic leukemia (also classified NHL in our cohort) [1]. Future examinations of lymphoma incidence among persons with HBV infection should consider rates according to cell type.

Typically unlisted as a cancer category in studies examining associations between HBV infection and nonliver cancers, the incidence of malignant NE tumors in the hepatitis B cohort was significantly higher than in the general population; the SRR was the second highest of all non-HCC cancers. Regarded historically as rare and affiliated with inherited endocrine disorders, the incidence of NE tumors has been increasing (partially attributable to improved diagnostics), and 95% occur in persons without these inherited conditions [14]. To our knowledge, there have been no reports of increased rates of NE tumors among persons with HBV infection in the literature, although there have been several case reports, including 1 reporting detection of HBV DNA in a pancreatic NE tumor [15]. Nonetheless, there were 7 incident NE malignancies in this hepatitis B cohort during 2006–2018. These cancers were diagnosed independently at each of the 4 study sites; among the cases, these tumors arose primarily in the gastrointestinal tract and lungs.

As with hematologic malignancies and lymphomas, our classification of NE cancers in this analysis was based on tumor histology/morphology rather than anatomic site. Thus, we classified the 2 pulmonary NE and 2 pancreatic NE incident cancers as NE rather than lung or pancreatic cancers, which were comprised of several (non-NE) histologic/morphologic types. Often considered indolent and nonlethal, a recent analysis of SEER data involving approximately 74 000 patients diagnosed with NE cancers from 1973 to 2014 reported a median survival of 41 months [14]. As with other cancers, survival depends on extent of disease at diagnosis; nonmetastatic tumors can be cured with surgical removal, and medical treatments are available for metastatic illness [14]. Of the 7 hepatitis B cohort patients with incident NE cancers, 1 with a pulmonary NE tumor died 2 years after diagnosis and lung cancer was listed as an underlying cause.

The principal limitation of this analysis was the relatively low number of incident cancers in our hepatitis B cohort compared with those in the national registries, which resulted not only in wide 95% CIs for incidence rates, but more importantly, meant that incremental changes in the number of incident cases of a particular cancer in the hepatitis B cohort could substantially affect the incidence rate. The latter phenomenon probably

favored higher rates in the hepatitis B cohort, and the comparatively large number of patients in the national registries favored the detection of statistical differences between the 2 cohorts. Unlike the national registry data, our hepatitis B cohort was not population based; thus, our findings may not be generalizable to all hepatitis B patients and settings. Furthermore, we could not control for other factors that could affect cancer incidence, such as behavioral risk factors (eg, smoking, alcohol), obesity, metabolic disorders, or hepatitis B disease activity and treatment. Although we intended to record incident primary cancers in the hepatitis B cohort, it was possible that some prevalent or recurrent cancers were misclassified and inadvertently included. As it was not feasible to exclude HBV-infected persons from the national registries, rate calculations for the general population thus included a (low) number of persons with HBV infection, which would reduce apparent differences in rates between our cohort and the general population.

In summary, we found substantially increased rates of several cancers in our hepatitis B cohort compared with the US population. Some of these, including HCC, cholangiocarcinoma, NHL, and gastric cancer, have been characterized similarly by other investigators; others, including ovarian and NE cancer, have not. Rates of renal, pancreatic, colorectal, breast, lung/bronchus, and thyroid cancer were only modestly increased compared to the US population. In addition to surveillance for HCC, clinicians caring for HBV-infected patients should be aware of the potential risk of nonliver cancers, as earlier diagnosis favors improved survival. Future investigations of this topic should consider examination of NE cancer incidence, as well as delineation of rates for specific types of NHL, such as DLBCL.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Chronic Hepatitis Cohort Study (CHeCS) investigators. Eyasu H. Teshale, Philip R. Spradling, Anne C. Moorman, Jim Xing, and Yuna Zhong, Division of Viral Hepatitis, National Centers for HIV, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia; Stuart C. Gordon, Mei Lu, Lois Lamerato, Jia Li, Loralee B. Rupp, Nonna Akkerman, Nancy Oja-Tebbe, Talan Zhang, Sheri Trudeau, and Yueren Zhou, Henry Ford Health System, Detroit, Michigan; Joseph A. Boscarino, Zahra S. Daar, and Robert E. Smith, Center for Health Research, Geisinger Health System, Danville, Pennsylvania; Yihe G. Daida and Carmen P. Wong, The Center for Integrated Health Care Research, Kaiser Permanente-Hawaii, Honolulu, Hawaii; and Mark A. Schmidt, Judy L. Donald, and Erin M. Keast, The Center for Health Research, Kaiser Permanente-Northwest, Portland, Oregon.

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