original reports

Association of Chronic Hepatitis B Infection and Antiviral Treatment With the Development of the Extrahepatic Malignancies: A Nationwide Cohort Study

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abstract

PURPOSE Epidemiologic studies suggest that chronic hepatitis B (CHB) is a risk factor for various primary extrahepatic malignancies. Our aim was to evaluate the associations of CHB and nucleos(t)ide analog (NA) treatment with the risk of the development of extrahepatic malignancies.

PATIENTS AND METHODS We conducted an 18-month landmark analysis using nationwide claims data from the National Health Insurance Service of South Korea. Patients newly diagnosed with CHB in 2012-2014 (n = 90,944) and matched-controls (n = 685,436) were included. Patients with CHB were further classified as the NA-treated (CHB+/NA+, n = 6,539) or the NA-untreated (CHB+/NA–, n = 84,405) group. Inverse probability of treatment weighting analysis was applied to balance the treatment groups. Time-varying Cox analysis was performed to evaluate time-varying effect of NA treatment. The primary outcome was the development of any primary extrahepatic malignancy. Development of intrahepatic malignancy and death were considered as competing events.

RESULTS During the study period (median = 47.4 months), 30,413 patients (3.9%) developed any extrahepatic malignancy. The CHB+/NA– group had a higher overall risk of extrahepatic malignancy than the CHB+/NA+ group (adjusted subdistribution hazard ratio [aSHR] = 1.28; 95% CI, 1.12 to 1.45; $P < .001$) or controls (aSHR = 1.22; 95% CI, 1.18 to 1.26; $P < .001$). There was no difference in the risk of extrahepatic malignancy between the CHB+/NA+ group and the controls (CHB+/NA+ *v* control: aSHR = 0.96; 95% CI, 0.84 to 1.08; $P = .48$). In time-varying Cox analysis, the CHB+/NA– patients were associated with a higher risk of extrahepatic malignancy than the CHB+/NA+ patients (aSHR = 1.37; 95% CI, 1.23 to 1.52; $P < .001$).

CONCLUSION Patients with CHB have an elevated risk of developing primary extrahepatic malignancy. Long-term NA treatment was associated with a lower risk of extrahepatic malignancy development among patients with CHB.

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INTRODUCTION

Chronic hepatitis B (CHB) is the most common chronic viral infection in the world.[1] According to the Global Burden of Disease Study 2017, CHB causes 700 thousand deaths per year, approximately half of which involve intrahepatic malignancy.[2] Hepatitis B virus (HBV) causes intrahepatic malignancy via direct (HBV DNA integration in the host genome or transactivation of host oncogenes by HBV proteins) and indirect (chronic inflammation because of recurrent hepatocyte injury and regeneration) mechanisms.[3-5] Anti-HBV treatment with nucleos(t)ide analogs (NAs) that block HBV replication and suppress viral load can decrease the risk of hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma by up to 45%-63%[6-8] and 54%,[9] respectively, although risk reduction was significant mostly among cirrhotic patients.

Recent epidemiologic studies reported associations between HBV infection and the risk of primary extrahepatic malignancies.[10-12] In addition, HBV DNA particles were detected in cancer tissues of breast and central nervous system,[13] and HBV X (HBx) protein was highly expressed in stomach and pancreatic cancers.[11] Local inflammation was detected in extrahepatic tissues where HBV DNA was detected.[14-17] Nevertheless, it is unclear whether NA treatment for CHB reduces the risk of extrahepatic malignancy in patients with CHB.

This study aimed to evaluate the associations of CHB and NA treatment with the risk of the development of extrahepatic malignancies. We compared the cumulative risks of primary extrahepatic malignancies in subjects without CHB (the control group), patients with CHB who did not receive NA treatment (the CHB+/

ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Our aim was to evaluate the associations of chronic hepatitis B (CHB) and nucleos(t)ide analog treatment with the risk of the development of extrahepatic malignancies.

Knowledge Generated

Patients with CHB had an elevated risk of developing primary extrahepatic malignancy. By contrast, long-term nucleos(t)ide analog treatment was associated with lower risk of extrahepatic malignancy development among patients with CHB.

Relevance

More attention to the higher risk of extrahepatic malignancy in patients with CHB is needed than in the general population.

NA– group), and patients with CHB who received NA treatment (the CHB+/NA+ group).

PATIENTS AND METHODS

Data Source

A retrospective cohort was constructed using nationwide claims registered in the South Korean National Health Insurance Service (NHIS) database from January 1, 2010, to December 31, 2018. The NHIS is a health insurance program covering 97% of South Korean population.[18,19] Diagnoses in the NHIS database are based on the International Classification of Diseases, 10th revision (ICD-10). Details of data obtained from each individual are provided in the Data Supplement (online only). The NHIS regularly audits ICD-10 codes, procedure records, and prescription records to avoid unnecessary medical expense,[20] and analyzing the use of this database for research purposes has been validated externally[21] and internally.[22] The institutional review boards of the NHIS (No. NHIS-2019-1-638) and Seoul National University Hospital (No. 2001-115-1096) approved the current study. The requirement for informed consent was waived because of the retrospective nature of the study and because all clinical data were anonymous.

Study Populations and NA Treatment

In the 2012-2014 NHIS database, 144,440 South Korean patients with CHB were included in the study. Any oral anti-HBV NA available in 2012 in South Korea (tenofovir disoproxil fumarate, entecavir, lamivudine, telbivudine, adefovir, or clevudine) was considered an NA treatment. The specific drug and the duration of NA treatment were determined using claimed prescription codes. The cumulative defined daily dose (DDD) was defined according to the Anatomic Therapeutic Chemical classification system and the DDD Index 2020.[23] A total of 22,772 patients who were prescribed an NA within the 2 years before cohort entry were excluded.[24] To avoid reverse causation and immortal-time bias, we used a landmark analysis[25,26] with a prior exposure period of 18 months from the cohort entry date.

The participants were divided into three groups: the CHB+/NA– group, CHB+/NA+ group, and control group. The CHB+/NA– patients were newly diagnosed with CHB between 2012 and 2014, and received no NA treatment or had NA treatment for < 72 days within the first 90 days during the exposure period. The CHB+/NA+ patients were newly diagnosed with CHB between 2012 and 2014, and who were prescribed an NA for at least 72 days consecutively within the first 90 days of the 18-month exposure period. The controls were selected from a population of individuals who were not diagnosed with CHB but visited any hospital for other causes between 2012 and 2014. Individuals in the CHB groups and the control group were matched at a 1:5.1 ratio. The control group was selected by using multiway stratification method (Data Supplement). We also established a 2-year washout period to exclude individuals who met exclusion criteria (Data Supplement). For the patients with CHB, the cohort entry date was set as the date when CHB was first diagnosed. For the controls, the date of a randomly selected hospital visit between 2012 and 2014 was assigned as the cohort entry date. The index date was set as 18 months after the cohort entry date. During the 18-month exposure period, 7,429 patients with CHB and 13,323 controls were excluded because of death, malignancy development, or transplantation.

The remaining 90,944 patients with CHB (6,539 with NA treatment and 84,405 without NA treatment) and 685,436 controls (Appendix Fig A1, online only) constituted the final study sample.

Outcomes

The primary outcome was the development of any extrahepatic malignancy. Extrahepatic malignancy diagnosis was defined as patients who had a claimed diagnosis code of extrahepatic malignancy (ICD-10 codes: C00-C97 except C22). Only the first diagnosed cancer after the index date was considered an event. Metastasis from prior primary intrahepatic malignancy during the study period was also considered as one of the competing events along with death and diagnosis of new intrahepatic malignancy.

Secondary outcomes were the specific development of any of the 10 most common extrahepatic malignancies in South Korea: stomach, colorectal, lung, thyroid, breast, prostate, pancreas, gallbladder and biliary tract, kidney cancer, and non-Hodgkin lymphoma. The date of cancer diagnosis was defined as the date of the first claim with the designated ICD-10 cancer code.

Statistical Analysis

Continuous variables were presented as the mean and standard deviation or median and interquartile range (IQR). Categorical variables were presented in terms of No. (%). The Kolmogorov-Smirnov test was performed to ascertain the normality of continuous variables. To ensure a balanced analysis, inverse probability of treatment weighting (IPTW) was used. All measured variables were included in the IPTW calculation. Standardized differences in means were calculated to evaluate the quality of balancing before and after IPTW. Follow-up began from the index date and lasted until the date of extrahepatic malignancy diagnosis, any competing event, or the end of the study period, whichever came first. The end of the study period was December 31, 2018. In parallel to landmark analysis, time-varying Cox analysis was performed to evaluate the time-dependent effect[27] of NA on developing extrahepatic malignancy (Data Supplement). Incidences of primary and secondary outcome were estimated in terms of events per 100 or 1,000 person-years. To estimate the effect of covariates on the cumulative incidence, while considering competing risks, we calculated adjusted subdistribution hazard ratios (aSHRs) using the Fine-Gray model.[28] *P* value for interaction ($P_{interaction}$) was calculated to evaluate whether NA treatment had differential effects on extrahepatic malignancies according to respective subgroups.[29]

Various sensitivity analyses were conducted. (1) By using different landmark points form the cohort entry date (12 months [781,693 subjects] and 24 months [771,042 subjects] for models 1A and 1B, respectively), additional cohorts were established and analyzed. (2) Different statistical approaches were applied for validation: Analysis of the IPTW unadjusted 18-month landmark cohort (model 2A) and cause-specific analysis that treated competing events as censoring events[30] (model 2B) were done. (3) In a subcohort (433,148 subjects, the NHIS Health Check-Up Database) for whom additional health check-up data including laboratory data, anthropometric measures, and findings from a lifestyle questionnaire (smoking, alcohol, and physical exercise) were available, IPTW was used again by using those additional variables and sensitivity analysis was conducted (model 3). (4) To minimize detection bias, another sensitivity analysis was conducted in the model adjusted for the frequency of hospital visits (model 4; Data Supplement).

Additional information about the data source and statistical approach is provided in the Data Supplement. Data Supplement Table 1 summarizes the diagnostic, procedural, and prescription codes used in the analyses. SAS Enterprise Guide 7.1 (SAS Institute Inc, Cary, NC) and R 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria) were used for all analyses. All statistical tests were two-sided with $P < .05$ as the threshold for significance.

RESULTS

Baseline Characteristics

The median follow-up duration was 47.4 months (IQR = 38.1-57.1 months). The baseline characteristics of the sample are shown in Table 1. After IPTW, the variables were generally well balanced among the study groups (Table 1 and Appendix Fig A2, online only). The follow-up period included a total of 3,045,997.6 person-years, during which 30,413 patients (3.9%) developed extrahepatic malignancy. The median cumulative DDD of NA during the 18-month exposure period was 450 days (IQR = 275-525 days) before IPTW and 443 days (IQR = 260-520 days) after IPTW (Table 2).

Incidence of Primary Extrahepatic Malignancy

On the 18-month landmark analysis, the event rate for the development of extrahepatic malignancy was 1.21 per 100 person-years in the CHB+/NA– group, 0.99 per 100 person-years in the CHB+/NA+ group, and 0.98 per 100 person-years in the control group (Table 2, Fig 1). For comparison, the incidences of intrahepatic malignancies were 0.52 per 100 person-years in the CHB+/NA– group, 0.45 per 100 person-years in the CHB+/NA+ group, and 0.09 per 100 person-years in the control group (Appendix Fig A3, online only). The CHB+/NA– group had higher overall risk of extrahepatic malignancy than the CHB+/NA+ group (aSHR = 1.28; 95% CI, 1.12 to 1.45; $P < .001$) and the control group (aSHR = 1.22; 95% CI, 1.18 to 1.26; $P < .001$). There was no difference in the risk of extrahepatic malignancy between the CHB+/NA+ patients and controls (aSHR = 0.96; 95% CI, 0.84 to 1.08; $P = .48$).

The results were similar within most subgroups with comparable aSHR across age and coexisting medical conditions (Table 3). However, a difference in the effects of NA was noticed between female and male subgroups ($P_{interaction} = .01$), between respective socioeconomic status subgroups ($P_{interaction} = .004$), and between patients with and without hypertension ($P_{interaction} = .04$).

In time-varying Cox analysis in CHB+ groups, the CHB+/NA– patients had a higher risk of extrahepatic malignancy than the CHB+/NA+ patients (aSHR = 1.37; 95% CI, 1.23 to 1.52; $P < .001$; Table 4), like in the landmark analysis.

Sensitivity Analyses

Various sensitivity analyses were performed and showed consistent results as shown in Table 5. In the IPTW-balanced 12-month landmark data set (model 1A; Data Supplement Table 2), the CHB+/NA– patients had a higher risk of extrahepatic malignancy than the CHB+/NA+ patients (aSHR = 1.22; 95% CI, 1.08 to 1.39; $P = .002$) and

TABLE 1. Baseline Characteristics of the 18-Month Landmark Cohort Before and After IPTW

Characteristic	Before IPTW						After IPTW[a]					
				Standardized Difference[b]						Standardized Difference[b]		
	Controls (α; n = 685,436)	CHB+/NA– (β; n = 84,405)	CHB+/NA+ (γ; n = 6,539)	β v α	γ v β	α v γ	Controls (α; n = 682,590)	CHB+/NA– (β; n = 82,462)	CHB+/NA+ (γ; n = 6,286)	β v α	γ v β	β v α
Age, median (IQR), years	51 (42-59)	50 (41-58)	47 (40-54)	–.03	–.25	–.28	51 (42-58)	51 (42-59)	50 (42-57)	.01	–.08	–.07
Male, No. (%)	375,535 (54.8)	43,316 (51.3)	4,084 (62.5)	–.07	.22	.15	371,555 (54.4)	44,360 (53.8)	3,383 (53.8)	–.01	< .01	–.01
Socioeconomic status,[c] No. (%)				.04	.08	.06				.02	.02	.03
High	230,057 (33.6)	27,445 (32.5)	2,130 (32.6)				228,161 (33.4)	27,461 (33.3)	2,032 (32.3)			
Middle	298,122 (43.5)	36,931 (43.8)	2,998 (45.9)				297,340 (43.6)	35,790 (43.4)	2,765 (44.0)			
Low	112,272 (16.4)	14,183 (16.8)	1,057 (16.2)				112,136 (16.4)	13,581 (16.5)	1,055 (16.8)			
Medical Aid	24,914 (3.6)	3,622 (4.3)	197 (3.0)				25,203 (3.7)	3,295 (4.0)	249 (4.0)			
Others[d]	20,071 (2.9)	2,224 (2.6)	157 (2.4)				19,750 (2.9)	2,334 (2.8)	185 (3.0)			
Level of health care, No. (%)				.49	.46	.96				.17	.02	.16
Tertiary	28,806 (4.2)	9,889 (11.7)	1,380 (21.1)				34,052 (5.0)	4,360 (5.3)	336 (5.3)			
Secondary	62,665 (9.1)	16,341 (19.4)	1,983 (30.3)				70,705 (10.4)	8,908 (10.8)	687 (10.9)			
Primary	76,405 (11.2)	10,316 (12.2)	839 (12.8)				77,169 (11.3)	9,676 (11.7)	753 (12.0)			
Clinic	502,959 (73.4)	47,756 (56.6)	2,333 (35.7)				487,674 (71.4)	59,339 (72.0)	4,494 (71.5)			
Health center	14,601 (2.1)	103 (0.1)	4 (0.1)				12,990 (1.9)	179 (0.2)	17 (0.3)			
Coexisting medical conditions												
Cirrhosis, No (%)	28,748 (4.2)	7,629 (9.0)	905 (13.8)	.20	.15	.34	30,334 (4.4)	4,199 (5.1)	311 (4.9)	.03	–.01	.02
Decompensated cirrhosis, No. (%)	27,664 (4.0)	5,007 (5.9)	342 (5.2)	.09	–.03	.06	28,967 (4.2)	3,726 (4.5)	269 (4.3)	.01	–.01	< .01
Ascites, No. (%)	6,140 (0.9)	1,250 (1.5)	118 (1.8)	.05	.03	.08	6,528(1.0)	888 (1.1)	49 (0.8)	.01	–.03	–.02
Varices, No. (%)	22,227 (3.2)	4,037 (4.8)	252 (3.9)	.08	–.05	.03	23,254 (3.4)	2,950 (3.6)	226 (3.6)	.01	< .01	.01
Diabetes mellitus, No. (%)	97,832 (14.3)	15,976 (18.9)	854 (13.1)	.13	–.16	–.04	100,529 (14.7)	13,452 (16.3)	1,051 (16.7)	.04	.01	.05
Hypertension, No. (%)	170,472 (24.9)	23,500 (27.8)	1,186 (18.1)	.07	–.23	–.16	171,520 (25.1)	21,878 (26.5)	1,648 (26.2)	.03	–.01	.03
CCI,[e] mean ± SD, points	0.7 ± 1.2	0.7 ± 1.2	0.6 ± 1.1	.22	–.09	.13	0.5 ± 1.0	0.5 ± 1.0	0.5 ± 1.0	.06	–.02	.04

Abbreviations: CCI, Charlson comorbidity index; CHB, chronic hepatitis B; IPTW, inverse probability of treatment weighting; IQR, interquartile range; NA, nucleos(t)ide analog; SD, standard deviation.

[a]Propensity scores were computed by using following variables: age, sex, socioeconomic status, level of health care, cirrhosis, decompensated cirrhosis, ascites, varices, diabetes mellitus, hypertension, and CCI.

[b]α, control; β, NA-untreated (CHB+/NA–); γ, NA-treated (CHB+/NA+).

[c]High, middle, and low socioeconomic status indicate socioeconomic status of ≥ 75th percentile, 25th-75th percentile, and < 25th percentile, respectively.

[d]Population with a special occupation such as military personnel or shipping labor union.

[e]Patients' CCIs were acquired 1 year before the cohort entry date.

the controls (aSHR = 1.24; 95% CI, 1.20 to 1.27; $P < .001$) with no difference between latter two groups (aSHR = 1.01; 95% CI, 0.89 to 1.15; $P = .82$). The results were the same for the IPTW-balanced 24-month landmark data set (model 1B, Data Supplement Table 3), the IPTW-unadjusted 18-month landmark cohort (model 2A), and the cause-specific analysis of the IPTW-balanced 18-month landmark data set (model 2B; Appendix Fig A4, online only).

In the subcohort of NHIS Health Check-Up Database (model 3; Data Supplement Table 4), our main result was maintained: CHB+/NA– patients had a higher risk of extrahepatic malignancy than both CHB+/NA+ patients (aSHR = 1.23; 95% CI, 1.05 to 1.45; $P = .01$) and the control subjects (aSHR = 1.17; 95% CI, 1.13 to 1.22; $P < .001$), but there was no difference between the CHB+/NA+ patients and the control subjects (CHB+/NA+ *v*

TABLE 2. Unadjusted Outcomes and Cox Proportional Hazard Analysis After Inverse Probability of Treatment Weighting

Group Analyzed	Median cDDDs Use of NA (IQR), days	No.	Events	Median Follow-Up (IQR), years	Crude Incidence, per 100 Person-Year	SHR (95% CI)			
						Univariable	*P*	Multivariable[a]	*P*
Other groups *v* controls									
Controls		682,590	26,005	3.9 (3.2-4.7)	0.98 (0.97-0.99)	Reference		Reference	
CHB+/NA–		82,462	4,090	4.3 (3.3-5.0)	1.21 (1.18-1.25)	1.22 (1.18 to 1.26)	< .001	1.22 (1.18 to 1.26)	< .001
CHB+/NA+	443 (260-520)	6,286	244	4.1 (3.1-5.0)	0.99 (0.87-1.12)	0.95 (0.84 to 1.08)	.440	0.96 (0.84 to 1.08)	.480
NA– *v* NA+									
CHB+/NA+						Reference		Reference	
CHB+/NA–						1.28 (1.12 to 1.45)	< .001	1.28 (1.12 to 1.45)	< .001

Abbreviations: cDDD, cumulative daily defined dose; CHB, chronic hepatitis B; IQR, interquartile range; NA, nucleos(t)ide analog; SHR, subdistribution hazard ratio.

[a]Adjusted for level of health care.

control: aSHR = 0.95; 95% CI, 0.81 to 1.11; $P = .53$). When we conducted subgroup analyses in this subcohort, the results were consistent in most subgroups (Data Supplement Table 5). However, there were significant differences in aSHR among the hypertension subset ($P_{interaction} = .007$) and among the ascites subset ($P_{interaction} = .01$).

The median frequencies of hospital visits were 15.3, 15.9, and 11.7 times per person per year in the CHB+/NA–, CHB+/NA+, and control groups, respectively, which were significantly different ($P < .001$). When hospital visits were adjusted (model 4), our main result was consistently reproduced.

Incidence of Specific Extrahepatic Malignancies

As shown in the Data Supplement Table 6, compared with controls, CHB+/NA– patients had higher risks of stomach cancer (aSHR = 1.27; 95% CI, 1.16 to 1.41; $P < .001$), lung cancer (aSHR = 1.13; 95% CI, 1.01 to 1.26; $P = .03$), thyroid cancer (aSHR = 1.25; 95% CI, 1.12 to 1.38; $P < .001$), prostate cancer (aSHR = 1.23; 95% CI, 1.13 to 1.34; $P < .001$), pancreatic cancer (aSHR = 1.64; 95% CI, 1.46 to 1.84; $P < .001$), gallbladder cancer (aSHR = 1.63; 95% CI, 1.37 to 1.94; $P < .001$), kidney cancer (aSHR = 1.25; 95% CI, 1.03 to 1.52; $P = .03$), and non-Hodgkin lymphoma (aSHR = 1.92; 95% CI, 1.50 to 2.44; $P < .001$). Compared with controls, CHB+/NA+ patients had increased risks of breast cancer (aSHR = 1.61; 95% CI, 1.13 to 2.28; $P = .007$) and kidney cancer (aSHR = 2.03; 95% CI, 1.21 to 3.41; $P < .001$).

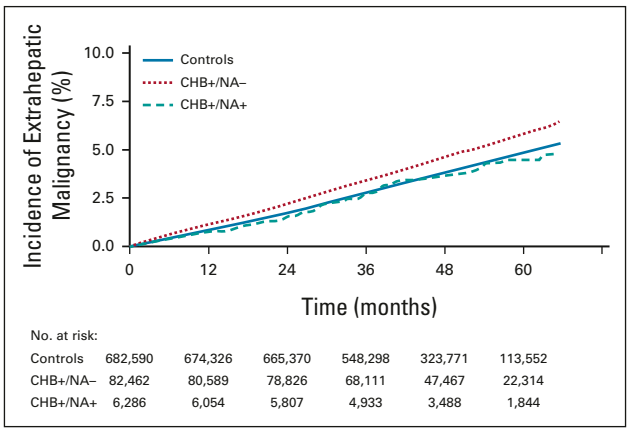

FIG 1. Weighted cumulative incidence of primary extrahepatic malignancies (18-month landmark analysis). The analysis was performed after IPTW, and extrahepatic malignancy development, metastasis, and death were treated as competing risks. Propensity scores for IPTW were computed using the following variables: age, sex, socioeconomic status, level of health care, cirrhosis, decompensated cirrhosis, ascites, varices, diabetes mellitus, hypertension, and Charlson comorbidity index. CHB, chronic hepatitis B; IPTW, inverse probability of treatment weighting; NA, nucleos(t)ide analog.

As shown in the Data Supplement Table 7, the CHB+/NA– group had higher risks of prostate cancer (aSHR = 1.69; 95% CI, 1.15 to 2.50; $P = .006$) and pancreatic cancer (aSHR = 2.44; 95% CI, 1.35 to 4.35; $P = .003$), and lower risk of breast cancer than the CHB+/NA+ group (aSHR = 0.60; 95% CI, 0.41 to 0.86; $P = .005$).

DISCUSSION

The CHB+/NA– group had a 22% higher risk of extrahepatic malignancy than the control and a 28% higher risk of extrahepatic malignancy than the CHB+/NA+ group in our landmark analysis at 18 months. By contrast, the risk of extrahepatic malignancy in the CHB+/NA+ group was comparable with that of the control group. Robust analyses were feasible owing to a large data set established by the South Korean NHIS. Our findings were consistent after multiple statistical methods, including landmark analysis, time-varying Cox analysis, and IPTW, were applied to minimize bias such as immortal-time bias.

There are several mechanisms by which HBV infection might increase the risk of extrahepatic malignancy. The viral protein HBx was detected in stomach and pancreatic cancers,[11] which suggests that direct HBV-induced carcinogenesis might occur in organs other than liver.[3,5]

TABLE 3. Risk of Extrahepatic Malignancy According to Prespecified Subgroups

	Events/Subjects			CHB+/NA– (*v* controls)		CHB+/NA+ (*v* controls)		CHB+/NA– (*v* CHB+/NA+)		
Factor	CHB+/NA–	CHB+/NA+	Controls	aSHR (95% CI)[a]	*P*	aSHR (95% CI)[a]	*P*	aSHR (95% CI)[a]	*P*	$P_{interaction}$[b]
Age, years										.070
≥ 65 (n = 105,888)	1,158/11,536	38/573	7,598/93,779	1.16 (1.09 to 1.24)	< .001	0.73 (0.53 to 1.01)	.06	1.56 (1.34 to 2.17)	.005	
< 65 (n = 665,450)	2,931/70,926	206/5,713	18,407/588,811	1.23 (1.18 to 1.28)	< .001	1.08 (0.94 to 1.24)	.26	1.14 (0.99 to 1.32)	.070	
Sex										.010
Male (n = 419,299)	2,309/44,360	117/3,383	14,448/371,555	1.25 (1.20 to 1.31)	< .001	0.84 (0.70 to 1.01)	.06	1.49 (1.23 to 1.79)	< .001	
Female (n = 352,039)	1,781/38,101	126/2,903	11,557/311,035	1.19 (1.13 to 1.25)	< .001	1.10 (0.92 to 1.31)	.30	1.09 (0.90 to 1.30)	.380	
Socioeconomic status[c]										.004
High (n = 257,655)	1,469/27,461	63/2,032	9,020/228,161	1.26 (1.19 to 1.33)	< .001	0.73 (0.57 to 0.94)	.01	1.72 (1.33 to 2.22)	< .001	
Middle (n = 335,894)	1,606/35,790	99/2,765	10,315/297,340	1.22 (1.15 to 1.28)	< .001	0.97 (0.80 to 1.19)	.79	1.25 (1.02 to 1.54)	.030	
Low (n = 177,789)	1,015/19,211	82/1,489	6,670/157,089	1.17 (1.10 to 1.25)	< .001	1.21 (0.98 to 1.51)	.08	0.97 (0.78 to 1.22)	.780	
Level of health care										.780
Tertiary (n = 38,748)	203/4,360	14/336	1,481/34,052	0.92 (0.80 to 1.07)	.300	0.86 (0.51 to 1.45)	.57	1.08 (0.63 to 1.85)	.790	
Secondary (n = 80,299)	408/8,908	26/687	3,137/70,705	0.95 (0.86 to 1.05)	.340	0.78 (0.53 to 1.15)	.22	1.22 (0.81 to 1.82)	.340	
Primary[d] (n = 652,291)	3,479/69,194	204/5,264	21,387/577,833	1.29 (1.24 to 1.33)	< .001	0.99 (0.86 to 1.14)	.89	1.30 (1.12 to 1.49)	< .001	
Cirrhosis										.840
No (n = 764,494)	3,814/78,262	229/5,975	24,383/652,256	1.22 (1.18 to 1.27)	< .001	0.96 (0.85 to 1.10)	.59	1.27 (1.11 to 1.45)	< .001	
Compensated cirrhosis (n = 1,883)	28/474	2/42	106/1,367	0.59 (0.39 to 0.90)	.020	0.62 (0.17 to 2.22)	.46	0.96 (0.25 to 3.57)	.960	
Decompensated cirrhosis (n = 32,961)	248/3,726	12/269	1.516/28,967	1.19 (1.04 to 1.36)	.010	0.81 (0.46 to 1.41)	.45	1.47 (0.83 to 2.63)	.190	
Ascites										.690
No (n = 763,874)	4,022/81,573	240/6,237	25,545/676,063	1.22 (1.18 to 1.27)	< .001	0.96 (0.84 to 1.09)	.50	1.28 (1.12 to 1.45)	< .001	
Yes (n = 7,464)	68/888	3/49	460/6,528	1.04 (0.80 to 1.34)	.780	0.98 (0.34 to 2.84)	.97	1.06 (0.36 to 3.13)	.920	
Varices										.490
No (n = 744,908)	3,899/79,511	235/6,060	24,896/659,337	1.22 (1.18 to 1.26)	< .001	0.96 (0.85 to 1.10)	.57	1.27 (1.11 to 1.45)	< .001	
Yes (n = 26,430)	190/2,950	9/226	1,109/23,254	1.26 (1.08 to 1.47)	.003	0.78 (0.41 to 1.50)	.46	1.61 (0.83 to 3.13)	.160	
Diabetes mellitus										.970
No (n = 656,308)	3,086/69,011	182/5,235	19,737/582,062	1.24 (1.19 to 1.29)	< .001	0.97 (0.83 to 1.12)	.64	1.28 (1.11 to 1.49)	< .001	
Yes (n = 115,031)	1,004/13,452	62/1,051	6,268/100,529	1.11 (1.04 to 1.19)	.002	0.87 (0.68 to 1.12)	.27	1.28 (0.99 to 1.64)	.060	
Hypertension										.040
No (n = 576,292)	2,539/60,584	137/4,638	16,002/511,071	1.25 (1.20 to 1.31)	< .001	0.88 (0.75 to 1.04)	.15	1.43 (1.19 to 1.69)	< .001	
Yes (n = 195,046)	1,551/27,878	107/1,649	10,003/171,520	1.13 (1.07 to 1.19)	< .001	1.04 (0.86 to 1.26)	.70	1.09 (0.89 to 1.33)	.390	
CCI, points										.410
≥ 3 (n = 40,748)	410/4,320	27/304	2,642/36,123	1.18 (1.06 to 1.31)	.002	1.08 (0.74 to 1.59)	.68	1.09 (0.74 to 1.61)	.670	
< 3 (n = 730,590)	3,680/78,141	217/5,982	23,363/646,467	1.23 (1.18 to 1.27)	< .001	0.94 (0.83 to 1.08)	.41	1.30 (1.14 to 1.49)	< .001	

Abbreviations: aSHR, adjusted subdistribution hazard ratio; CCI, Charlson comorbidity index; CHB, chronic hepatitis B; NA, nucleos(t)ide analog; $P_{interaction}$, *P* value for interaction.

[a]Adjusted for level of health care.

[b]$P_{interaction}$ was calculated between CHB+/NA+ and CHB+/NA– patients.

[c]High, middle, and low socioeconomic status indicate socioeconomic status of ≥ 75th percentile, 25th-75th percentile, and < 25th percentile or medical aid, respectively.

[d]Primary subgroup includes primary level hospital, clinic, and health center.

TABLE 4. Time-Varying Cox Analysis Comparing CHB+/NA– and CHB+/NA+ Patients

Group Analyzed	No.	Events	Median Follow-Up (IQR), years	Incidence, per 100 Person-Year	SHR (95% CI)[a]			
					Univariable	*P*	Multivariable[b]	*P*
CHB+/NA+	11,443	392	4.2 (2.5-5.5)	0.87 (0.79-0.96)	Reference		Reference	
CHB+/NA–	92,447	4,313	5.4 (4.2-6.4)	0.95 (0.92-0.98)	1.29 (1.16 to 1.43)	< .001	1.37 (1.23 to 1.52)	< .001

Abbreviations: CHB, chronic hepatitis B; IQR, interquartile range; NA, nucleos(t)ide analog; SHR, subdistribution hazard ratio.

[a]The CHB+/NA+ patients were defined as those who were prescribed NA for at least 72 days consecutively within the first 90 days among patients with CHB. The CHB+/NA– patients were defined as patients who had CHB, but did not meet the CHB+/NA+ criteria (ie, NA-naive patients or patients who were prescribed NA for < 72 days within the first 90 days).

[b]Adjusted for level of health care.

Furthermore, chronic inflammation was observed around HBV-infected stomach, kidney, and pancreatic tissues,[14-17] which suggests that HBV-induced inflammation might contribute to carcinogenesis outside the liver.[4,5] During chronic HBV infection, dendritic cells display functional impairment,[31,32] which leads to dysfunction of natural killer (NK) cells.[33] One prospective study reported that the activity of peripheral NK cells was inversely correlated with the risk of malignancies.[34] Together, these results suggest that decreased NK cell function might play a role in extrahepatic malignancy development.

NAs block viral polymerase and suppress HBV replication.[35] By complete suppression of HBV replication, NA treatment lowers the likelihood of malignant transformation and local inflammation. In addition, restoration of host immune system after NA treatment[36] enhances immune surveillance of tumor cells. Clinical studies showed that the HBV viral load was positively correlated with HCC development, and that suppression of HBV replication reduced the risk of intrahepatic malignancy development in a time- and dose-dependent manner.[6-8,37] Specifically, considering cirrhotic patients with low-level viremia has residual risk of HCC,[37] complete viral suppression is a critical factor in preventing HCC. A similar protective mechanism in extrahepatic malignancy prevention is possible as our study showed that complete HBV suppression by NA treatment was associated with a lower risk of extrahepatic malignancy. Since host genome integration of HBV in extrahepatic malignancies has not been evident,[13] it is theoretically possible that the anticarcinogenic effect of complete suppression of HBV could be more profound in extrahepatic malignancies than in intrahepatic malignancies, to which additional risk of cancer from integrated HBV contributes. However, this hypothesis needs further clinical and experimental studies for validation.

However, NA treatment showed differential effects on preventing extrahepatic malignancy between hypertensive and normotensive subgroups, even after balancing potential confounders in the subcohort of NHIS Health Check-Up Database. Although there might be a multiplicity issue resulting in a high probability of false-positive findings,[38] it is notable that the hypertensive subgroup consistently showed significantly different results compared with the normotensive subgroup. Currently, there seems to be no plausible explanation for the differential effect of NA according to the presence or absence of hypertension, and further studies to address this different effect in hypertensive patients are needed. The differential effect of NA was noticed also in the ascites subset of the subcohort, unlike in that of the entire cohort. However, caution is needed in interpreting this result, given that only 31 CHB+/NA+ patients were included in the ascites subgroup.

Among CHB patients who received NA treatment had lower risks of pancreas and prostate cancers but higher risk of breast cancer than patients who did not receive NA treatment. Pancreatic stellate cells and acinar cells, like hepatocytes, express sodium taurocholate cotransporting polypeptide receptor,[39,40] which acts as a direct entry site for HBV.[41] HBV infection of pancreatic cells via sodium taurocholate cotransporting polypeptide receptor might enable carcinogenesis similar to that induced by HBV in liver cells. HBV infection of acinar cells can cause local inflammation,[16] which might also play a role in pancreatic cancer development. HBV has not been detected in prostate tissue,[42] and neither NAs nor HBV has been shown to alter the testosterone levels. Immune suppression is a major risk factor for prostate cancer,[43] however, and innate immune suppression by HBV might increase the risk of prostate cancer, which would be ameliorated by NA treatment. Breast cancer has been linked to substances that mimic estrogen,[44] and some NAs were reported to cause gynecomastia in male patients, possibly because of estrogen mimicry,[45] which might explain the increased risk of breast cancer in patients who received NA treatment in our study. Surveillance for breast cancer in patients with CHB treated with NA might be advisable.

Our study has several limitations. First, the NHIS database does not contain the serum level of HBV DNA or HBV envelope antigen and antibody of each patient, which made it difficult to interpret whether hepatitis B viral status might be a confounding factor in developing extrahepatic malignancy. However, the patients in the CHB+/NA+ group are expected to achieve nonviremic status before landmark time at 18 months, considering the efficacy of NA as proven in randomized controlled studies.[46-48] By contrast, although the degree of replication of HBV is expected

TABLE 5. Results of Sensitivity Analyses

Group Analyzed	Median cDDDs Use of NA (IQR), days	No.	Events	Median Follow-Up (IQR), years	Incidence, per 100 Person-year	SHR (95% CI)[a] Univariable	*P*	Multivariable	*P*
Analysis of different landmark points									
Model 1A: 12-month landmark cohort									
Other groups *v* controls									
Controls		686,560	28,581	4.4 (3.6-5.2)	0.95 (0.94-0.97)	Reference		Reference	
CHB+/NA–		84,414	4,591	4.7 (3.8-5.6)	1.20 (1.17-1.24)	1.23 (1.19 to 1.27)	< .001	1.24 (1.20 to 1.27)[b]	< .001
CHB+/NA+	318 (222-353)	5,559	247	4.6 (3.6-5.5)	1.02 (0.90-1.16)	1.01 (0.89 to 1.14)	.880	1.01 (0.89 to 1.15)[b]	.820
NA– *v* NA+									
CHB+/NA+						Reference		Reference	
CHB+/NA–						1.22 (1.08 to 1.39)	.002	1.22 (1.08 to 1.39)[b]	.002
Model 1B: 24-month landmark cohort									
Other groups *v* controls									
Controls		678,523	23,230	3.4 (2.7-4.2)	1.00 (0.99-1.02)	Reference		Reference	
CHB+/NA–		80,712	3,573	3.8 (2.9-4.6)	1.22 (1.18-1.26)	1.20 (1.15 to 1.24)	< .001	1.20 (1.16 to 1.24)[b]	< .001
CHB+/NA+	557 (316-690)	6,861	248	3.8 (2.7-4.6)	1.03 (0.91-1.16)	0.97 (0.86 to 1.10)	.660	0.98 (0.86 to 1.11)[b]	.720
NA– *v* NA+									
CHB+/NA+						Reference		Reference	
CHB+/NA–						1.23 (1.08 to 1.39)	.002	1.23 (1.08 to 1.39)[b]	.002
Different statistical approaches									
Model 2A: crude population before using IPTW									
Other groups *v* controls									
Controls		685,436	26,082	3.9 (3.2-4.7)	0.98 (0.97-0.99)	Reference		Reference	
CHB+/NA–		84,405	4,107	4.3 (3.4-5.1)	1.18 (1.15-1.22)	1.18 (1.14 to 1.22)	< .001	1.17 (1.13 to 1.21)[c]	< .001
CHB+/NA+	450 (275-525)	6,539	224	4.2 (3.1-5.1)	0.86 (0.76-0.98)	0.83 (0.73 to 0.94)	.005	0.96 (0.84 to 1.09)[c]	.520
NA– *v* NA+									
CHB+/NA+						Reference		Reference	
CHB+/NA–						1.43 (1.25 to 1.64)	< .001	1.22 (1.06 to 1.39)[c]	.005
Model 2B: cause-specific analysis									
Other groups *v* controls									
Controls		682,590	26,005	3.9 (3.2-4.7)	0.98 (0.97-0.99)	Reference		Reference	
CHB+/NA–		82,461	4,090	4.3 (3.3-5.0)	1.21 (1.18-1.25)	1.23 (1.19 to 1.28)	< .001	1.24 (1.20 to 1.28)[b]	< .001
CHB+/NA+	443 (260-520)	6,286	244	4.1 (3.1-5.0)	0.99 (0.87-1.12)	1.00 (0.84 to 1.20)	.970	1.01 (0.84 to 1.21)[b]	.930

(continued on following page)

TABLE 5. Results of Sensitivity Analyses (continued)

Group Analyzed	Median cDDDs Use of NA (IQR), days	No.	Events	Median Follow-Up (IQR), years	Incidence, per 100 Person-year	SHR (95% CI)[a]			
						Univariable	*P*	Multivariable	*P*
NA– *v* NA+									
CHB+/NA+						Reference		Reference	
CHB+/NA–						1.23 (1.02 to 1.47)	.030	1.23 (1.02 to 1.47)[b]	.030
Model 3: NHIS Health Check-Up Database									
Other groups *v* controls									
Controls		378,715	15,549	3.9 (3.2-4.7)	1.06 (1.04-1.07)	Reference		Reference	
CHB+/NA–		48,663	2,511	4.3 (3.3-5.0)	1.26 (1.22-1.31)	1.17 (1.12 to 1.22)	< .001	1.17 (1.13 to 1.22)[d]	< .001
CHB + NA+	450 (258-521)	3,929	154	4.2 (3.2-5.0)	0.99 (0.84-1.16)	0.89 (0.76 to 1.04)	.130	0.95 (0.81 to 1.11)[d]	.530
NA– *v* NA+									
CHB+/NA+						Reference		Reference	
CHB+/NA–						1.32 (1.12 to 1.56)	< .001	1.23 (1.05 to 1.45)	.010
Model 4: hospital visit-adjusted model									
Other groups *v* controls									
Controls		682,590	26,005	3.9 (3.2-4.7)	0.98 (0.97– 0.99)	Reference		Reference	
CHB+/NA–		82,461	4,090	4.3 (3.4-5.1)	1.21 (1.18-1.25)	1.22 (1.18 to 1.26)	< .001	1.18 (1.14 to 1.22)[e]	< .001
CHB+/NA+	443 (260-520)	6,286	244	4.2 (3.1-5.1)	0.99 (0.87-1.12)	0.95 (0.84 to 1.08)	.440	0.92 (0.81 to 1.04)[e]	.190
NA– *v* NA+									
CHB+/NA+						Reference		Reference	
CHB+/NA–						1.28 (1.12 to 1.44)	< .001	1.28 (1.14 to 1.47)[e]	< .001

Abbreviations: cDDD, cumulative daily defined dose; CHB, chronic hepatitis B; IPTW, inverse probability of treatment weighting; IQR, interquartile range; NA, nucleos(t)ide analog; NHIS, National Health Insurance Service; PPPY, per person per year; SHR, subdistribution hazard ratio.

[a]For model 2B, hazard ratios (instead of SHRs) are provided.

[b]Adjusted for level of health care.

[c]Adjusted for age, sex, socioeconomic status, level of health care, cirrhosis, decompensated cirrhosis, ascites, varices, diabetes mellitus, hypertension, and Charlson comorbidity index in multivariable analysis.

[d]Adjusted for level of health care, age, and serum level of triglyceride in multivariable analysis.

[e]The median hospital visit frequency was 15.3 times PPPY in the CHB+/NA– group, 15.9 times PPPY in the CHB+/NA+ group, and 11.7 times PPPY in the control group. The frequency of hospital visits (PPPY) adjusted as a covariate in the Fine-Gray model along with level of health care.

to be heterogeneous, the CHB+/NA– group represents patients with persistent HBV viremia.[49,50] Thus, the key difference between the CHB+/NA+ and CHB+/NA– groups might be whether patients achieved complete viral suppression or not. Therefore, the finding that the CHB+/NA+ group had a lower risk of extrahepatic malignancy than the CHB+/NA– group might possibly result from the complete suppression of HBV achieved by long-term NA treatment in the CHB+/NA+ group. Second, it should be acknowledged that our study design was not suitable to compare the risk of intrahepatic malignancy between the CHB+/NA+ and CHB+/NA– groups. In previous studies, the preventive effect of NA on both HCC and intrahepatic cholangiocarcinoma was significant among cirrhotic patients, but not among noncirrhotic patients in the previous studies that demonstrated significant effect.[6,7,9] As the baseline characteristics of the CHB+/NA+ and CHB+/NA– groups were balanced with the control group, the prevalence of cirrhosis in this study (4.4%-5.1%) was substantially lower than that in previous studies (13%-26%) and consequently, the preventive effect might have been underestimated. Third, detection bias in a cancer study is inevitable. More extrahepatic malignancies could be detected earlier during more frequent hospital visit among patients with CHB than controls.[51] Even so, the CHB+/NA+ group showed comparable risk to the control group, which might be contrary to the general situation of the detection bias, given that the CHB+/NA+ group visited hospital more frequently than the control groups. Moreover, we established a model adjusted for hospital visits to minimize detection bias and confirmed that the main result was reproduced even in this model. Fourth, owing to the retrospective nature of this study, potential selection bias cannot be completely ruled out. To minimize selection bias, multiple statistical methods such as IPTW and multivariable analysis were applied to balance and adjust baseline characteristics of three groups. In the subcohort (NHIS Health Check-Up Database) of the study population, health check-up data including laboratory data,[52] anthropometric data,[53] and lifestyle-related factors such as smoking[54] and alcohol consumption,[55] which are well-known risk factors for various cancers, were available. In a sensitivity analysis, we confirmed that the direction of the original result was maintained even after additionally balancing those specific variables from the subcohort. Randomized controlled trials might be warranted to explore whether NA treatment will reduce the risk of extrahepatic malignancy in patients with CHB outside the current treatment indication. Finally, it needs to be further validated in multinational or multiethnicity studies if our results are reproducible in other ethnicities[56] and patients infected with HBV genotype other than genotype C, which is a major genotype in South Korea.[57]

In conclusion, HBV infection was associated with increased risk of primary extrahepatic malignancies. NA treatment was associated with a lower incidence of various primary extrahepatic malignancies in patients with CHB. Patients with CHB should be advised to participate in screening program for major cancers.

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DISCLAIMER

The corresponding author (J.-H.L.) 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.

EQUAL CONTRIBUTION

D.H.L., S.W.C., and J.-H.L. equally contributed as cofirst authors to this work.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Association of Chronic Hepatitis B Infection and Antiviral Treatment With the Development of the Extrahepatic Malignancies: A Nationwide Cohort Study

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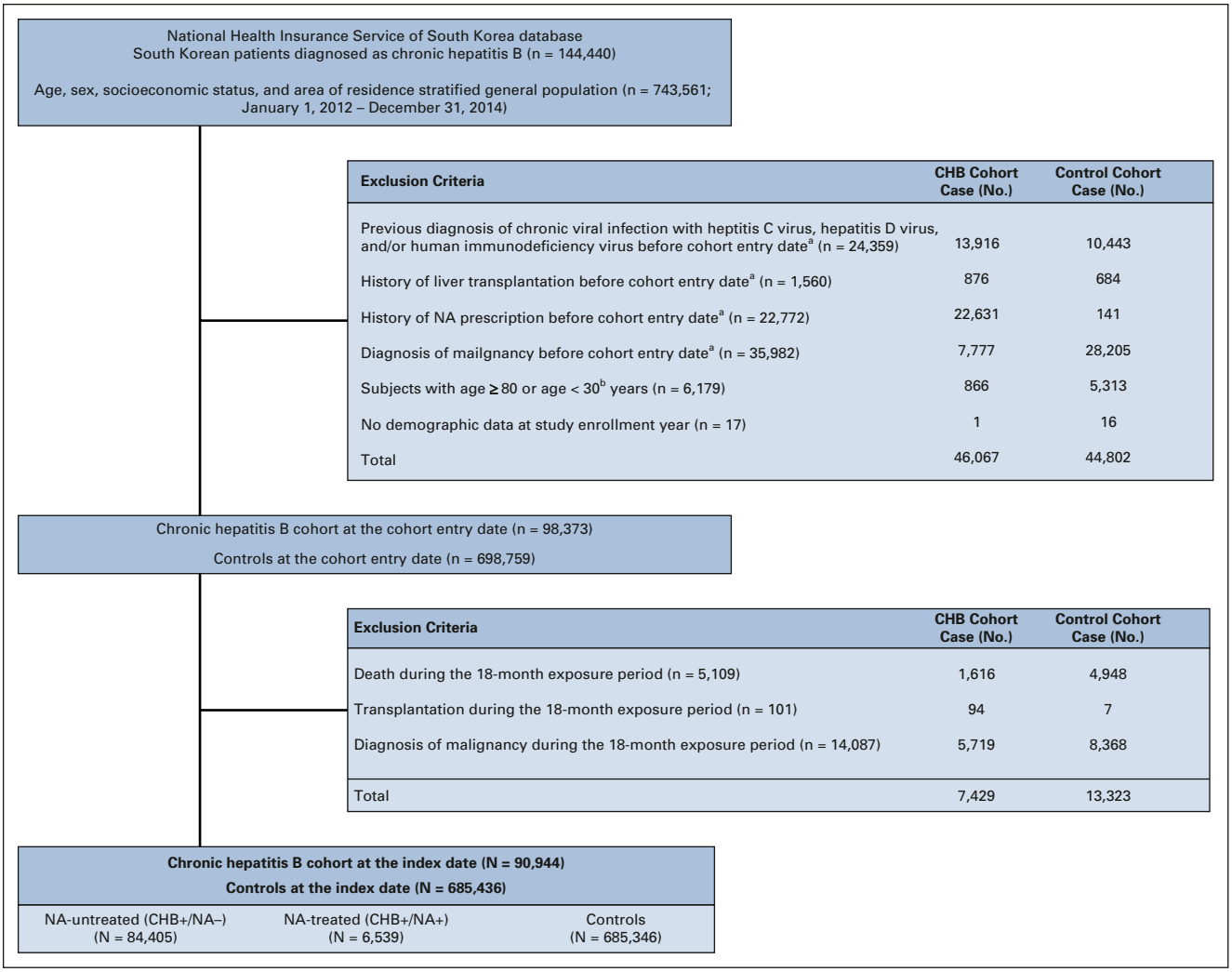
APPENDIX



Exclusion Criteria	CHB Cohort Case (No.)	Control Cohort Case (No.)
Previous diagnosis of chronic viral infection with heptitis C virus, hepatitis D virus, and/or human immunodeficiency virus before cohort entry date[a] (n = 24,359)	13,916	10,443
History of liver transplantation before cohort entry date[a] (n = 1,560)	876	684
History of NA prescription before cohort entry date[a] (n = 22,772)	22,631	141
Diagnosis of mailgnancy before cohort entry date[a] (n = 35,982)	7,777	28,205
Subjects with age ≥ 80 or age < 30[b] years (n = 6,179)	866	5,313
No demographic data at study enrollment year (n = 17)	1	16
Total	46,067	44,802

Exclusion Criteria	CHB Cohort Case (No.)	Control Cohort Case (No.)
Death during the 18-month exposure period (n = 5,109)	1,616	4,948
Transplantation during the 18-month exposure period (n = 101)	94	7
Diagnosis of malignancy during the 18-month exposure period (n = 14,087)	5,719	8,368
Total	7,429	13,323

FIG A1. Patient flow diagram. [a]Specific diagnostic and procedural codes are listed in the Data Supplement Table 1. [b]Missing data imputation was performed by using intrasubject nearest data. CHB, chronic hepatitis B; NA, nucleos(t)ide analog.

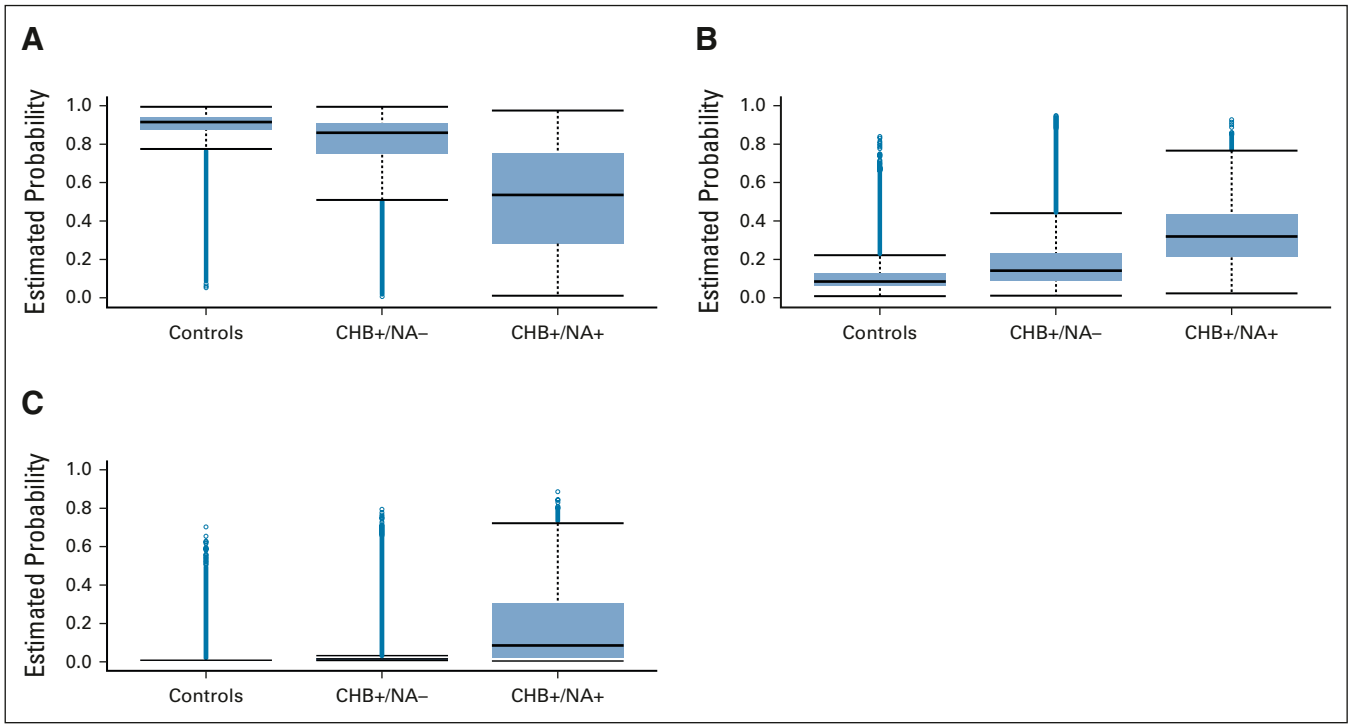


FIG A2. Distribution of propensity scores of the (A) control, (B) CHB+/NA−, and (C) CHB+/NA+ groups. Propensity scores were computed using the following variables: age, sex, socioeconomic status, level of healthcare, cirrhosis, decompensated cirrhosis, ascites, varices, diabetes mellitus, hypertension, and Charlson comorbidity index. CHB, chronic hepatitis B; NA, nucleos(t)ide analog.

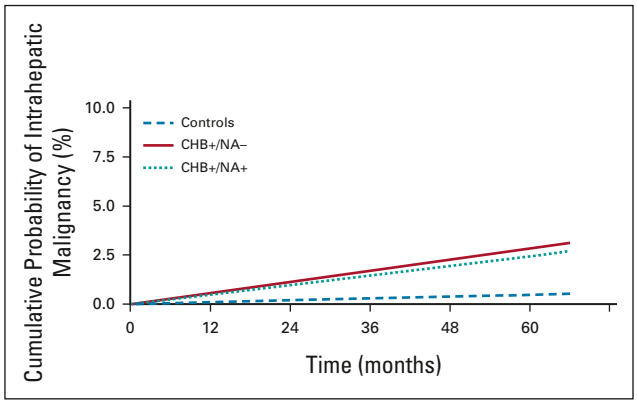


FIG A3. Cumulative probability of intrahepatic malignancies. Analysis was performed after inverse probability of treatment weighting and extrahepatic malignancy development, metastasis, and death were treated as competing risks. Propensity scores for inverse probability weighting were computed using the following variables: age, sex, socioeconomic status, level of healthcare, cirrhosis, decompensated cirrhosis, ascites, varices, diabetes mellitus, hypertension, Charlson comorbidity index, and the frequency of alpha-fetoprotein test and abdominal imaging were used as covariates. A cause-specific model was applied for analysis and the calculated incidences of intrahepatic malignancies were 0.52 per 100 person-years in the CHB+/NA− group, 0.45 per 100 person-years in the CHB+/NA+ group, and 0.09 per 100 person-years in the control group. The CHB+/NA+ group had a lower risk of intrahepatic malignancy development than the CHB+/NA− group (aSHR = 0.88, 95% CI = 0.77 to 1.01, $P = .08$) although it failed to reach statistical significance. CHB, chronic hepatitis B; NA, nucleos(t)ide analog.

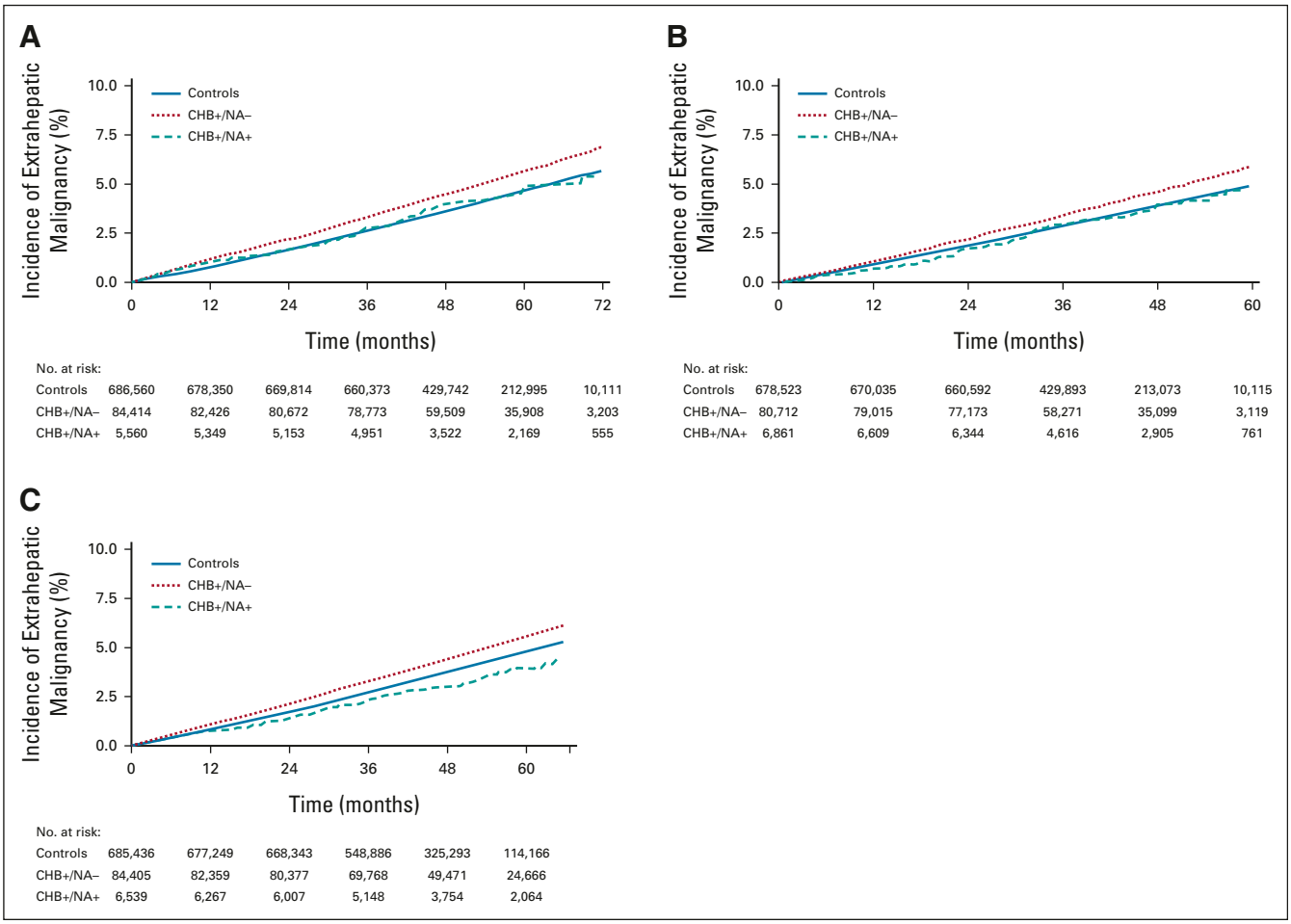


FIG A4. Cumulative incidence of extrahepatic malignancies according to different analyses: (A) 12-month landmark analysis,[a] (B) 24-month landmark analysis,[a] and (C) 18-month landmark analysis before inverse probability of treatment weighting. [a]Analysis was performed after inverse probability of treatment weighting and extrahepatic malignancy development, metastasis, and death were treated as competing risks. Propensity scores were computed using the following variables: age, sex, socioeconomic status, level of healthcare, cirrhosis, decompensated cirrhosis, ascites, varices, diabetes mellitus, hypertension, and Charlson comorbidity index. CHB, chronic hepatitis B; NA, nucleos(t)ide analog.