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Impact of nucleos(t)ide analog treatment on the development of malignancy in patients with chronic hepatitis B

Soon Sun Kim, MD, PhD[a], Eun Kyoung Ahn, RN, MPH[b], Soo Yeon Cho, RN, MPH[c], Rae Woong Park, MD, PhD[c], Hyo Jung Cho, MD, PhD[a], Ji-Hyun Kim, MD[a], Han Gyeol Kim, MD[a], Ga Ram Lee, MD[a], Sun Hyuk Hwang, MD[a], Min Jae Yang, MD[a], Jae Youn Cheong, MD, PhD[a], Sung Won Cho, MD, PhD[a,*]

Abstract

We evaluated whether nucleos(t)ide analog (NA) influences the risk of non-hepatocellular carcinoma (non-HCC) malignancies in patients with chronic hepatitis B (CHB). A total of 9867 patients with CHB were followed up for ≥12 months for the occurrence of any type of malignancy between 1998 and 2013. Patients who received NA for ≥180 days were defined as the NA group. Propensity score matching produced the control (n = 2220) and NA groups (n = 2220) after adjustment for age, sex, and the presence of diabetes mellitus and liver cirrhosis. The National Health Insurance Service sample cohort dataset was used for external validation. Regarding non-HCC malignancies, only old age was an independent risk factor (>50 years; hazard ratio 3.17, 95% confidence interval 1.71–5.88, $P < .001$) in multivariate analysis. With regard to specific cancers such as thyroid, breast, lung, stomach, colorectal, pancreatobiliary, and hematologic malignancy, there was no difference of the incidence of each malignancy between the NA and control groups in both the hospital-based and external validation cohorts. NA treatment neither raises nor lowers the incidence of non-HCC malignancies in patients with CHB. Patients >50 years old are encouraged to undergo surveillance for malignancies similar to the general population.

Abbreviations: CHB = chronic hepatitis B, CI = confidence interval, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HR = hazard ratio, IRB = institutional review board, NA = nucleos(t)ide analogs, NHIS = National Health Insurance Service.

Keywords: carcinoma, chronic, hepatitis B, hepatitis B virus, hepatocellular, incidence, neoplasms, nucleosides

1. Introduction

Since lamivudine was first approved as a hepatitis B virus (HBV) polymerase inhibitor, a number of nucleos(t)ide analogs (NAs) have been developed and widely used for the treatment of chronic hepatitis B (CHB).[1,2] Long-term viral suppression with NAs for the prevention of disease progression and improved survival is a current paradigm for antiviral therapy in patients with CHB.[3] Long-term treatment with NAs ameliorates histological abnormalities such as necroinflammation and/or fibrosis, both in hepatitis B e antigen-positive and hepatitis B e antigen-negative patients with CHB.[4,5] NA therapies also reduce the risk of developing hepatocellular carcinoma (HCC) in patients with CHB including CHB patients with cirrhosis.[6,7] Since the eradication of HBV infection is rarely achieved with NAs, long-term or lifelong treatment is necessary in most cases.

Meanwhile, several potential adverse effects of NAs have been reported including lactic acidosis, myopathy, acute renal failure, Fanconi syndrome, osteomalacia, neuropathy, and pancreatitis.[8] These adverse effects are, however, rarely reported, and NAs are generally accepted as well-tolerated and safe to use. Among NAs, entecavir had shown extrahepatic carcinogenic effects in animal experiments[9]; however, entecavir's influence on human carcinogenesis has not been reported worldwide. In addition, the discovery of HBV DNA in other organs suggests that HBV infection could increase the risk of extrahepatic cancers.[10,11] Associations between HBV infection and non-Hodgkin lymphoma, pancreatic cancer, and gastric cancer have been previously reported[12–14]; but, it is not clear if NAs used for the treatment of hepatitis B influence the risk of non-HCC malignancies.

The aim of this study was to assess the long-term effects of NAs on the risk of various malignancies in patients with CHB using a single university hospital-based cohort and a National Health Insurance Service (NHIS)-based sample cohort.

2. Materials and methods

2.1. Patient selection

We retrospectively enrolled 9867 consecutive patients with CHB treated at Ajou University Hospital, Suwon, South Korea between October 1998 and June 2013. CHB was defined as positive test results for hepatitis B surface antigen over a >6 months period of time. Patients were excluded if they met any of

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[a] Department of Gastroenterology, Ajou University School of Medicine, Suwon, [b] Department of Nursing, Dongyang University, Yeongju, [c] Department of Biomedical Informatics, Ajou University School of Medicine, Suwon, South Korea.

[*] Correspondence: Sung Won Cho, Department of Gastroenterology, Ajou University School of Medicine, 164, Worldcup-ro, Yeongtong-gu, Suwon, Gyeonggi-do 16499, South Korea (e-mail: sung_woncho@hotmail.com).

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the following criteria: age <19 years; evidence of autoimmune hepatitis or viral coinfection such as hepatitis C virus, hepatitis D virus, or human immunodeficiency virus; history of organ transplantation or bone marrow transplantation; history of HCC; history of any non-HCC malignancy other than HCC (excluding patients who had been free of cancer for >5 years after cure); and a diagnosis of any malignancy including HCC within the first year of observation, who were followed up for <12 months. Patients who received NAs for ≥180 days were defined as the NA group. NAs were considered to be used continuously only with blank period of ≤90 days. The blank period was not included in the NAs treatment day. Patients were followed up for the development of any type of new malignancy. Propensity score matching was performed at a ratio of 1:1 using adjustments for age, sex, and the presence of diabetes mellitus and liver cirrhosis. The institutional review board (IRB) of the Ajou University Hospital approved the study (IRB No. AJIRB-MED-EXP-15-447 and AJIRB-MED-MDB-16-134).

We used a sample cohort dataset provided by the NHIS[15] for external validation. These data corresponded to approximately 1 million individuals selected randomly from nearly the entire South Korean population, totaling 45 million people, with national claims data for the period from January 1, 2002 to December 31, 2013. The included variables were sex, 5-year age group, socioeconomic status (with subjects divided into 10 categories based on income), diagnosis code, surgery code, drug prescription data (drug name, dosage, and date of prescription), and billing code. We used the International Classification of Diseases 10th edition to extract the subjects with CHB (B18.0, B18.10, B18.18, B18.1, and Z22.5). Subjects diagnosed with acute viral hepatitis including hepatitis B (B15.X, B16.X, and B17.X) or other types of chronic viral hepatitis except hepatitis B (B18.2, B18.8, B18.9, and B19.X), patients coinfected with human immunodeficiency virus (Z21.X, Z86.X, B20.X, B21.X, B22.X, B23.X, and B24.X), and patients with a history of organ or bone marrow transplantation (Z94.X) were excluded. Subjects who were followed up for <1 year or subjects with a history of any malignancy or who developed any malignancy within the first year from the index date were excluded. Subjects <20 years old were also excluded. Among a total of 1,025,340 subjects, 9432 subjects were included for analysis (Supplementary Fig. 1, http://links.lww.com/MD/C289). The NA group was defined as those who were prescribed an NA (180901ATB [lamivudine], 457501ATB [adefovir dipivoxil], 487202ATB, 487202ATD, 487203ATB, and 487203ATD [entecavir], 548100ATB, 493901ATB, and 248100ATB [tenofovir disoproxil fumarate], and 506001ATB [telbivudine], 487801ACH, 487802ACH, and 487803ACH [clevudine]) for >180 days. The control group was matched to the NA group at a ratio of 5:1 using propensity score matching with adjustments for age, sex, and the presence of diabetes mellitus and liver cirrhosis. Subjects were investigated for the diagnosis of a malignancy other than HCC, specifically thyroid cancer (C73), breast cancer (C50.X), lung cancer (C34.X), stomach cancer (C16.X), colorectal cancer (C18.X, C19.X, and C20.X), biliary cancer (C22.1X, C23, and C24.X), pancreas cancer (C25.X), and hematologic malignancies (C81.X, C82.X, C83.X, C84.X, C85.X, C86.X, C88.X, C90.X, C91.X, C92.X, C93.X, C94.X, C95.X, and C96.X), at least 1 year after the index date.

2.2. Statistics

Data management and analysis were performed using the R statistical software (version 3.3.4; R Core Team [2014]; R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna Austria; URL http://www.R-project.org/). Significance was considered for P values <.05. All statistical analyses were performed using 2-tailed tests. Continuous variables were compared using independent samples t tests. Categorical data were compared using a Pearson χ^2 test or Fisher exact test. The cumulative probabilities of malignancies were assessed by Kaplan-Meier analysis. The Cox proportional hazard model was used to identify factors associated with the development of HCC or other malignancies.

3. Results

3.1. Baseline characteristics of the study population

Before propensity score matching, the control (n=7467) and NA groups (n=2400) showed different baseline characteristics in terms of all factors. After propensity scoring matching with adjustment for age, sex, and the presence of cirrhosis and diabetes mellitus at a ratio of 1:1, the control, and NA groups each consisted of 2220 subjects. The multivariate imbalance measure L1 decreased from 0.248 to <0.0001 after propensity score matching.[16] Despite propensity score matching, the NA group showed a lower platelet level, a higher international normalized ratio, a lower albumin, a higher bilirubin, and a higher alanine aminotransferase level compared to the control group (Table 1). Entecavir was the most frequently used single NA and was used in 1147 patients (51.7%) followed by lamivudine (15.7%) and

Table 1

Baseline characteristics of study population.

	Whole cohort			After propensity score matching		
	Control group (n=7467)	NA group (n=2400)	*P*	Control group (n=2220)	NA group (n=2220)	*P*
Age, y	41.7±12.4	42.2±10.7	.082	41.4±10.4	41.4±10.4	1.00
Sex, n (%)	4278 (57.3)	1737 (72.4)	.000	1619 (72.9)	1619 (72.9)	1.00
Platelet, $\times 10^9$/L	208.6±68.3	156.9±66.0	<.001	204.1±67.4	161.5±65.0	<.001
INR	1.09±0.24	1.20±0.35	<.001	1.11±0.26	1.19±0.34	<.001
Albumin, g/dL	4.2±0.5	4.0±0.6	<.001	4.3±0.5	4.0±0.5	<.001
Bilirubin, mg/dL	1.1±1.3	1.6±2.2	<.001	1.1±1.6	1.6±2.2	<.001
ALT, IU/L	70.4±255.9	204.6±288.0	<.001	69.8±242.8	212.2±295.3	<.001
Glucose, mg/dL	107.9±44.5	102.8±34.0	<.001	104.8±40.1	102.4±34.2	.06
Cirrhosis, n (%)	175 (2.3)	287 (12.0)	<.001	109 (4.9)	109 (4.9)	1.00
DM, n (%)	1010 (13.5)	222 (9.3)	<.001	190 (8.6)	190 (8.6)	1.00
Follow-up duration, days				1684 (365–5590)	1341 (365–5152)	

ALT=alanine aminotransferase, DM=diabetes mellitus, INR=international normalized ratio, NA=nucleos(t)ide analog.

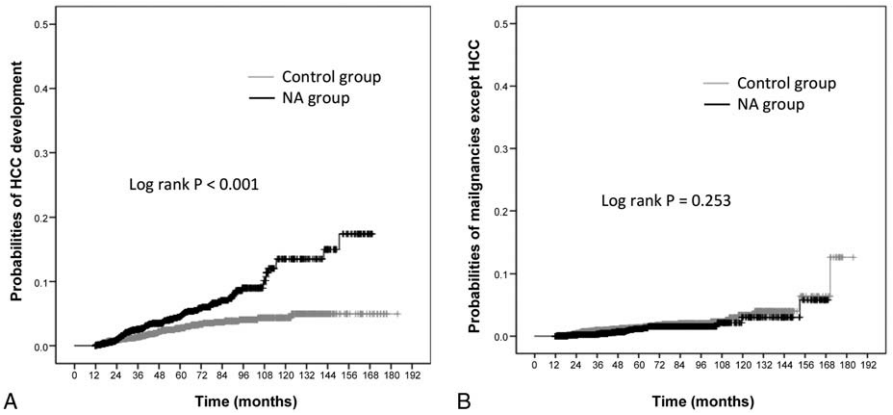

Figure 1. Cumulative probability for the development of malignancy in the control and NA groups. A, Probability of HCC in the control and NA groups. B, Probability of non-HCC malignancy in the control and NA groups. HCC = hepatocellular carcinoma, NA = nucleos(t)ide analog.

adefovir dipivoxil (1.7%). Approximately 30% of patients in the NA group were treated with 2 or more NAs (Supplementary Table 1, http://links.lww.com/MD/C289). The median follow-up period for the university hospital cohort was 1477 days (range, 365–5590 days), and the national sample cohort data were collected over a decade.

3.2. HCC development in the control and NA groups

Figure 1A shows the cumulative probabilities of HCC in the control and NA groups after propensity score matching using the Kaplan-Meier method. The NA group showed a higher probability of HCC development compared to the control group with a log-rank *P* value of <.001. However, multivariate analysis

Table 2

Factors associated with hepatocellular carcinoma development in cohort after propensity score matching.

Characteristics	Patients with HCC n = 148	Patients without HCC n = 4272	Univariate *P* value	Multivariate	
				Hazard ratio (95% CI)	*P*
Age ≥50 y, n (%)	78 (52.7)	856 (19.9)	<.001	3.43 (1.96–5.98)	<.001
Male sex, n (%)	117 (79.1)	3121 (72.7)	.21	2.06 (1.09–3.88)	.03
Cirrhosis, n (%)	31 (20.9)	187 (4.4)	<.001	2.07 (1.06–4.05)	.03
Diabetes mellitus, n (%)	26 (17.6)	352 (8.2)	<.001	1.18 (0.65–2.13)	.59
NA treatment, n (%)	94 (63.5)	2126 (49.5)	<.001	0.78 (0.45–1.37)	.39
Albumin, g/dL	3.7 (0.6)	4.2 (0.5)	<.001	0.80 (0.49–1.31)	.37
Bilirubin, mg/dL	1.9 (3.4)	1.3 (1.9)	.001	1.03 (0.95–1.11)	.51
ALT, IU/L	103.8 (123.7)	140.8 (282.6)	.99		
Platelet count, $\times 10^9$/L	121.2 (55.1)	187.7 (69.0)	<.001	0.90 (0.98–0.99)	<.001
INR	1.3 (0.3)	1.1 (0.3)	<.001	0.64 (0.21–1.91)	.42
AFP, ng/mL	33.0 (73.8)	114.5 (3353.2)	.93		

AFP = alpha fetoprotein, ALT = alanine aminotransferase, CI = confidence interval, HCC = hepatocellular carcinoma, INR = international normalized ratio, NA = nucleos(t)ide analog.

Table 3

Factors associated with whole malignancies development except hepatocellular carcinoma in cohort after propensity score matching.

Characteristics	Patients with malignancy n = 55	Patients without malignancy n = 4385	Univariate *P* value	Multivariate	
				Hazard ratio (95% CI)	*P*
Age ≥ 50 y, n (%)	22 (40.0)	912 (20.8)	.001	3.17 (1.71–5.88)	<.001
Male sex, n (%)	36 (65.5)	3202 (73.0)	.22	0.80 (0.43–1.50)	.49
Cirrhosis, n (%)	2 (3.6)	216 (4.9)	.77	1.00 (0.23–4.40)	.99
Diabetes mellitus, n (%)	7 (12.8)	373 (8.5)	.33	0.97 (0.38–2.49)	.94
NA treatment, n (%)	20 (36.4)	2200 (50.2)	.06	0.73 (0.35–1.51)	.40
Albumin, g/dL	4.1 (0.6)	4.2 (0.5)	.15		
Bilirubin, mg/dL	1.1 (0.9)	1.4 (1.9)	.29		
ALT, IU/L	110.1 (220.0)	140.0 (279.7)	.46		
Platelet count, $\times 10^9$/L	207.9 (72.1)	185.4 (70.0)	.03	1.00 (1.00–1.01)	.11
INR	1.1 (0.2)	1.1 (0.3)	.32		
AFP, ng/mL	9.0 (22.8)	112.3 (3303.7)	.89		

AFP = alpha fetoprotein, ALT = alanine aminotransferase, CI = confidence interval, HCC = hepatocellular carcinoma, INR = international normalized ratio, NA = nucleos(t)ide analog.

showed that only age (>50 years, hazard ratio [HR] 3.43, 95% confidence interval [CI] 1.96–5.98, $P < .001$), male sex (HR 2.06, 95% CI 1.09–3.88, $P = .03$), cirrhosis (HR 2.07, 95% CI 1.06–4.05, $P = .03$), and platelet level (HR 0.90, 95% CI 0.98–0.99, $P < .001$) were independent predictive factors for the development of HCC. NA treatment was not a risk factor for the development of HCC (HR 0.78, 95% CI 0.45–1.37, $P = .39$) (Table 2).

3.3. Non-HCC malignancies in the control and NA groups

In the Kaplan-Meier analysis, the cumulative probability of any non-HCC malignancy was not different between the control and

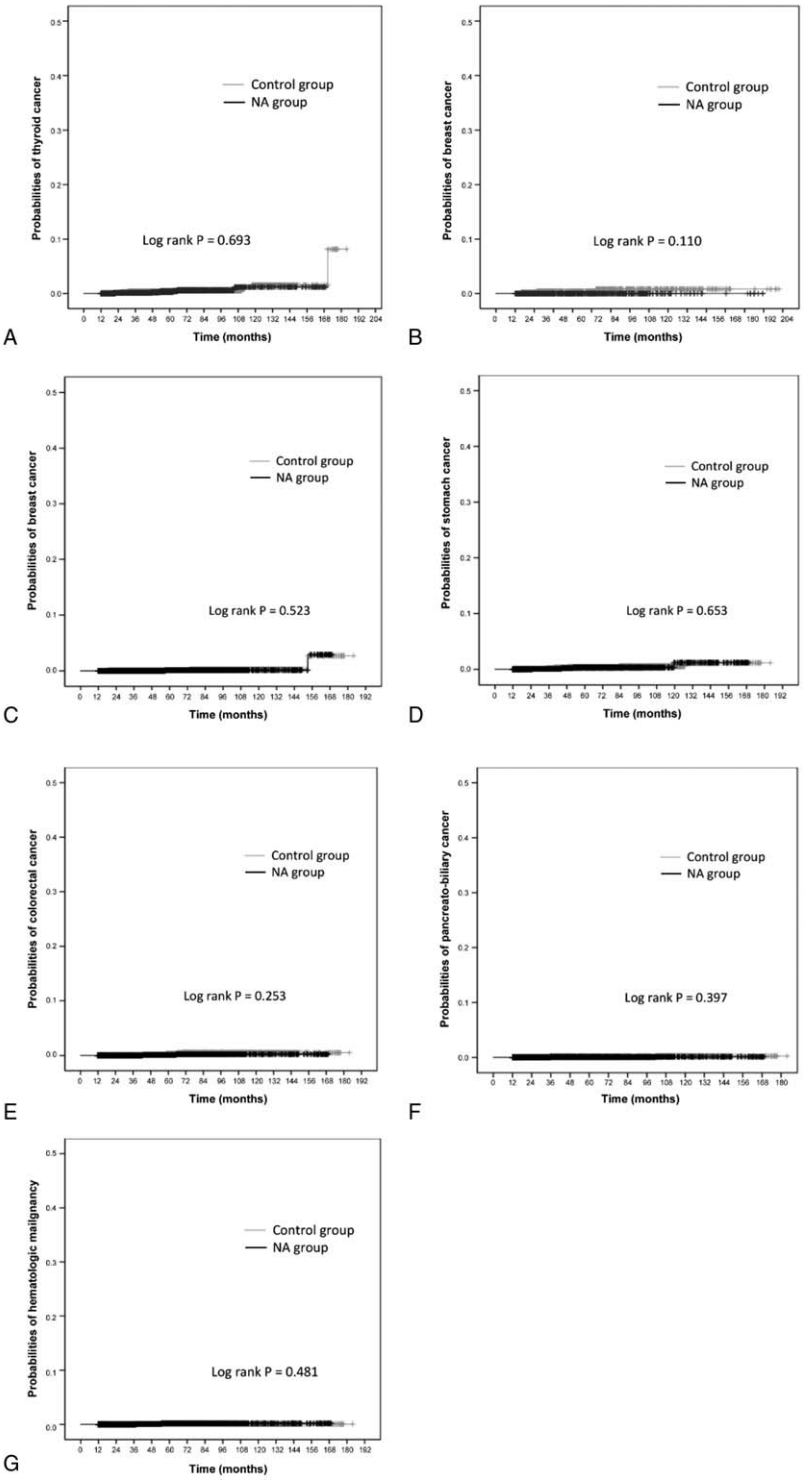

Figure 2. Cumulative probability of non-HCC in the control and NA groups. A, Thyroid cancer. B, Breast cancer. C, Lung cancer. D, Stomach cancer. E, Colorectal cancer. F, Pancreatobiliary cancer. G, Hematologic malignancies. HCC = hepatocellular carcinoma, NA = nucleos(t)ide analog.

NA groups (Fig. 1B). Multivariate analysis showed that only age >50 years was an independent risk factor for the development of non-HCC malignancy (HR 3.17, 95% CI 1.71–5.88, $P < .001$) (Table 3). With regard to specific cancers, there was no difference in the incidence of thyroid cancer, breast cancer, lung cancer, stomach cancer, colorectal cancer, pancreatobiliary cancer, and hematologic malignancy between the 2 groups (Fig. 2A–G). Subgroup analysis showed no significant association between entecavir and non-HCC malignancies (data not shown).

3.4. External validation using the NHIS sample cohort dataset

After propensity score matching for age, sex, and the presence of cirrhosis and diabetes mellitus, there were no statistically significant differences of baseline characteristics between the control group (n = 7859) and the NA group (n = 1573). There was no difference in the prevalence of thyroid cancer, breast cancer, lung cancer, stomach cancer, colorectal cancer, pancreatobiliary cancer, and hematologic malignancy between the 2 groups (Table 4).

Table 4

Factors associated to development of extrahepatic malignancies in National Health Insurance Service sample cohort dataset.

Type of malignancy	HR	95% CI	P
Overall			
Age >50	2.7	2.12–3.43	<.001
Female sex	0.99	0.78–1.26	.95
Cirrhosis	1.33	0.98–1.80	.07
Diabetes mellitus	1.23	0.94–1.63	.14
NA treatment	0.67	0.47–0.96	.03
Harrell's c-index = 0.634 (se = 0.017)			
Thyroid			
Age >50	0.9	0.42–1.93	.78
Female sex	3.08	1.66–5.70	<.001
Cirrhosis	1.70	0.75–3.89	.21
Diabetes mellitus	0.55	0.19–1.57	.26
NA treatment	0.98	0.44–2.20	.96
Harrell's c-index = 0.676 (se = 0.045)			
Breast*			
Age >50	1.04	0.38–2.84	.94
Cirrhosis	0.79	0.18–3.51	.76
Diabetes mellitus	1.41	0.45–4.45	.55
NA treatment	0.27	0.04–2.05	.21
Harrell's c-index = 0.577 (se = 0.064)			
Lung			
Age >50	8.4	4.67–15.11	<.001
Female sex	0.46	0.25–0.86	.02
Cirrhosis	1.246	0.62–2.5	.54
Diabetes mellitus	1.094	0.59–2.04	.78
NA treatment	0.562	0.22–1.41	.22
Harrell's c-index = 0.774 (se = 0.041)			
Stomach			
Age >50	2.36	1.31–4.24	.004
Female sex	0.47	0.24–0.92	.03
Cirrhosis	1.36	0.66–2.82	.41
Diabetes mellitus	1.59	0.84–3.00	.15
NA treatment	0.69	0.29–1.61	.39
Harrell's c-index = 0.674 (se = 0.042)			
Colorectal			
Age >50	3.03	1.87–4.93	<.001
Female sex	0.87	0.53–1.42	.57
Cirrhosis	1.79	1.02–3.16	.04
Diabetes mellitus	1.08	0.61–1.91	.79
NA treatment	0.57	0.26–1.24	.15
Harrell's c-index = 0.68 (se = 0.036)			
Pancreas			
Age >50	1.17	0.47–2.9	.73
Female sex	0.82	0.35–1.88	.63
Cirrhosis	0.52	0.12–2.24	.38
Diabetes mellitus	2.78	1.21–6.4	.02
NA treatment	0.68	0.20–2.26	.53
Harrell's c-index = 0.568 (se = 0.061)			
Hematologic			
Age >50	5.7	1.67–19.43	.005
Female sex	0.15	0.02–1.21	.08
Cirrhosis	1.37	0.29–6.45	.69
Diabetes mellitus	0.78	0.16–3.7	.75
NA treatment	1.21	0.26–5.62	.81
Harrell's c-index = 0.764 (se = 0.092)			

* Data were analyzed only in female.

CI = confidence interval, HR = hazard ratio, NA = nucleos(t)ide analog, NHIS = National Health Insurance Service.

4. Discussion

This study investigated the incidence of HCC and non-HCC malignancies in patients with CHB treated with or without NAs. The study included a single university hospital-based cohort and a national insurance–based sample cohort. We found that the incidence of thyroid, breast, lung, stomach, colon, pancreatobiliary cancer, and hematologic malignancy were not different between the control and NA groups.

Previous reports suggested that HBV infection can lead to an increased incidence of pancreatic cancer, stomach cancer, and bile duct cancer.[13,14,17,18] Therefore, we hypothesized that the incidence of these cancers would decrease with the administration of NA therapy because NA therapy has been shown to decrease the risk of HCC in patients with CHB.[6,7] On the contrary, as mentioned in the Introduction, entecavir increased the incidence of lung adenomas and carcinomas in male mice at exposures 3 times those used in humans and in female mice at exposures 40 times those used in humans. Brain gliomas were induced in both male and female rats at exposures 35 and 24 times dose of entecavir used in humans, respectively.[9] Therefore, there have been concerns regarding the extrahepatic carcinogenic effects of NAs, especially entecavir.

However, the current study showed no significant differences in the incidence of specific cancers including stomach and pancreatobiliary cancer between the control and NA groups in both the hospital-based cohort and the national insurance–based cohort, suggesting that NAs have no extrahepatic carcinogenic effect. In the hospital-based cohort, age >50 years was the only independent risk factor for the development of non-HCC malignancy (HR 3.17, 95% CI 1.71–5.88, $P < .001$). Advanced age is a well-known risk factor for several types of cancer including colorectal, lung, and prostate cancer, and screening is now recommended for the early detection of cancer in asymptomatic people ages > 50 to 55 years.[19] The results of the current study reaffirm that national cancer screening guidelines directed at the general population are also applicable to patients with CHB.

The incidence of HCC was higher in the NA group in the hospital-based cohort. This was an unexpected result that is at odds with those of previous reports. This result likely reflects the implicit nature of patients included in the NA group, who had poorer liver function than that of the control group and were more likely to receive NA treatment. Because of this, it is possible that the NA group showed a higher probability of HCC in the

Kaplan-Meier graph. Despite propensity score matching for age, sex, and the presence of cirrhosis and diabetes mellitus, the liver function profile of the NA group was worse than that seen in the control group. With multivariate analysis adjusting for other factors, NA treatment was not a risk factor for the development of HCC. In the national cohort, it was difficult to obtain detailed data such as platelet count, albumin level, and bilirubin level; therefore, the effect of NA treatment on the development of HCC could not be analyzed in the national cohort.

The present study has several limitations. First, the present study was a retrospective study based on subjects from a single tertiary hospital. Therefore, the NA group and the control group were not subject to the same intervals or methods for the screening of malignancies, especially extrahepatic malignancies. Despite the total duration of the study was long from 1998 to 2013, the mean follow-up period was short (1684 days and 1341 days in the NA and the control groups, respectively) and different between 2 groups. This discrepancy could bias the results of our study. Therefore, we attempted to validate the results using an external national sample cohort. Even though the national sample cohort included national health check data, specific liver function profiles could not be obtained in the majority of subjects. Therefore, liver functions could not be analyzed as a cofactor. However, the same results were obtained in the hospital cohort and the national cohort, so the results of this study may be reliable. Second, we did not compare the incidence of malignancies in patients with CHB to that of patients without CHB. Therefore, we could not determine the effect of HBV infection alone on the development of non-HCC malignancies. Third, only the first occurring cancer was included in the analysis. In other words, when a subject developed multiple cancers, only the first occurring malignancy was analyzed. This may have led to an underestimate of the incidence of malignancy or may have led to an incomplete assessment of the impact of NAs on the development of secondary malignancies.

In conclusion, HCC is the most common malignancy in patients with CHB. However, other malignancies also can develop in patients with CHB. Therefore, patients with CHB are encouraged to undergo surveillance for other malignancies in a manner similar to that used for the general population. Treatment with NAs neither raised nor lowered the incidence of non-HCC malignancies including thyroid, breast, lung, stomach, colorectal, pancreatobiliary, and hematologic malignancies.

Author contributions

Conceptualization: Rae Woong Park, Sung Won Cho.
Data curation: Eun Kyoung Ahn.
Formal analysis: Ji-Hyun Kim, Ga Ram Lee.
Investigation: Hyo Jung Cho.
Methodology: Soo Yeon Cho, Sun Hyuk Hwang.
Supervision: Min Jae Yang, Sung Won Cho.
Visualization: Han Gyeol Kim.
Writing – original draft: Soon Sun Kim.
Writing – review and editing: Jae Youn Cheong.

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