Synergistic Effects of Family History of Hepatocellular Carcinoma and Hepatitis B Virus Infection on Risk for Incident Hepatocellular Carcinoma

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Abstract

BACKGROUND & AIMS—Little is known about the effects of family history of hepatocellular carcinoma (HCC) on hepatitis B progression or risk of HCC. We examined how family HCC history and presence or stage of hepatitis B virus (HBV) infection affect risk for HCC.

METHODS—We performed a population-based cohort study of 22,472 participants from 7 townships in Taiwan who underwent evaluation for liver disease from 1991 through 1992. Those

who received a first diagnosis of HCC from January 1, 1991, to December 31, 2008, were identified from the Taiwanese cancer registry.

RESULTS—There were 374 cases of incident HCC over 362,268 person-years of follow-up evaluation. The cumulative risk of HCC in hepatitis B surface antigen (HBsAg)-seronegative patients without a family history of HCC was 0.62%, in those with a family history of HCC the cumulative risk was 0.65%, in HBsAg-seropositive patients without a family history of HCC the cumulative risk was 7.5%, and in HBsAg-seropositive patients with a family history of HCC the cumulative risk was 15.8% ($P < .001$). The multivariate-adjusted hazard ratio for HBsAg-seropositive individuals with family history, compared with HBsAg-seronegative individuals without a family history of HCC, was 32.33 (95% confidence interval, 20.8–50.3; $P < .001$). The relative excess risk owing to interaction was 19, the attributable proportion was 0.59, and the synergy index value was 2.54. These findings indicate synergy between family HCC history and HBsAg serostatus. The synergy between these factors remained significant in stratification analyses by HBeAg serostatus and serum level of HBV DNA.

CONCLUSIONS—Family history of HCC multiplies the risk of HCC at each stage of HBV infection. Patients with a family history of HCC require more intensive management of HBV infection and surveillance for liver cancer.

Keywords

Cirrhosis; Liver Disease; Epidemiology; Cancer Risk Factor

Hepatocellular carcinoma (HCC) is now the third leading cause of cancer mortality worldwide.[1,2] The prevalence and incidence of HCC is expected to continue to increase in the coming decades.[3,4] Despite advances in the pathogenesis and treatment of HCC, the death rates resulting from HCC continue to parallel the incidence rates.[5–8] Hepatitis B virus (HBV), a carcinogenic virus, is one of the leading causes of HCC worldwide.[9,10]

Patients infected with HBV are known to be at increased risk of HCC over their lifetime.[11–15] Previous studies have reported familial aggregation of HCC,[16,17] and recent meta-analyses have suggested that family history of HCC increases the risk of HCC in patients with viral hepatitis.[18] However, the interaction between family history of HCC and presence of hepatitis B surface antigen (HBsAg), HBV DNA levels, and presence or absence of hepatitis B e antigen (HBeAg) has not been elucidated systematically. Detailed epidemiologic investigation of interaction between familial risk and various stages of natural history of HBV infection would improve our understanding of pathways that lead to the development of HCC as well as prognostication for HCC within patients with HBV. Understanding prognostic factors and their interaction is especially of immense clinical importance in patients with HBV infection because they can develop HCC at each stage of HBV infection and do not necessarily need to have cirrhosis to develop HCC.[19] Risk stratification of HBV patients by such an approach would lead to refinement of HCC surveillance guidelines that could be personalized based on the status of family history of HCC and stage of HBV infection.

By using a large, well-characterized, prospective, community-dwelling cohort of participants with and without HBV infection, we conducted this study to examine whether the interaction between family history of HCC and various stages of HBV infection is synergistic in increasing the risk of incident HCC over 16 years of follow-up evaluation.

Methods

Study Participants

This study cohort was derived from the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/ Cancer-Hepatitis B Virus (REVEAL) study, which is a prospective cohort study that examines risk factors that increase the risk of incident HCC in participants with and without viral hepatitis.[20–22] Briefly, 47,079 male and 42,214 female residents (total, 89,293 residents) from 7 townships in Taiwan were invited to participate in a cancer screening program between 1991 and 1992. Among them, a total of 11,973 men (25%) and 11,847 women (28%) agreed to participate and provided written informed consent. Information on demographic and lifestyle factors was collected via a structured personal interview by well-trained public health nurses. Overnight fasting blood samples were collected at baseline, and tests on serum HBsAg, HBeAg, HBV DNA, and alanine aminotransferase levels were performed using commercial kits, and detailed laboratory procedures were followed as described previously.[11,20,21] The detailed description of the REVEAL cohort, study procedures, and protocol has been published previously.[11,20,21,23] Alcohol consumption was ascertained with the help of a questionnaire at the baseline visit.[22] Participants who tested positive for anti–hepatitis C antibodies were excluded. Participants were asked about their alcohol use (ever: yes/no), age at first use of alcohol, and present alcohol use (yes/no). Duration of alcohol use (in years) also was documented. Alcohol drinkers were defined as those who consumed alcohol at least 4 days per week for at least 1 year. All participants provided informed consent to participate in this study, and the data collection procedures were reviewed and approved by the Institutional Review Board of the College of Public Health at the National Taiwan University.

Exposure: Family History of Hepatocellular Carcinoma Status

Presence of family history was defined as having a first-degree relative with HCC. The family history status was ascertained with the help of a standardized questionnaire that was given to all participants at the baseline visit.

Hepatitis B Virus Infection Status

All participants underwent testing for HBsAg and those who were positive were classified as having HBV infection. To assess the effect of stages of natural history of hepatitis B, we further subclassified patients based on 2 key effect modifiers of HCC risk based on previous studies published using the REVEAL cohort: HBeAg status and the presence of high HBV DNA levels (10,000 copies/mL).[11,20] These 2 modifiers were chosen because HBeAg as well as HBV DNA independently and robustly predict HCC in patients with HBV.

We also assessed the presence of HBV genotype (whether genotype B vs genotype B/C or C) and also the presence of a basal core promoter mutation (wild type vs basal core promoter mutant) or the presence of a precore mutation (wild type vs precore mutation).

The following step-wise assessment was performed to assess the effect of each category and then all combined. Association between a family history of HCC, and (1) the presence (or absence) of HBsAg, (2) the presence (or absence) of HBeAg, and (3) the presence (or absence) of high HBV DNA levels.

Duration of Follow-up Evaluation

All of the 22,472 Taiwanese residents from 7 townships in Taiwan were followed up for a mean ± standard deviation of 16.12 ± 2.89 years (median ± interquartile range, 16.86 ± 0.83 y) for a first diagnosis HCC from January 1, 1991, to December 31, 2008.

Primary Outcome Measure: Hepatocellular Carcinoma

All participants who consented to participate in the study and underwent a baseline examination were followed up for development of HCC and were accounted for in the analyses. Participants with a prior diagnosis of HCC that was identified either by the national cancer registry or diagnosed with HCC during the baseline visit or from personal interview before or at enrollment were excluded from the analysis. All participants had a unique national identification number that was used to link with the computerized national cancer registry profiles in Taiwan to identify all the new HCC cases between January 1, 1991, and December 31, 2008. The Taiwan nationwide cancer registry system was initiated in 1978 and contains updated, accurate, and complete information on HCC. Because histologic confirmation of the HCC diagnosis was not reported in all the cases identified by the national cancer registry, adjudication of HCC diagnosis was performed by experts via chart reviews in those participants. This chart review was performed on 164 HCC cases in HBsAg-positive carriers to further confirm and validate the primary HCC diagnosis derived from the national cancer registry. All HCC cases included in this study must have met at least one of the following criteria endorsed by the American Association for the Study of Liver Diseases guidelines[24]: histopathologically confirmed HCC, detection and confirmation of HCC by at least 2 imaging tools (ultrasonography, angiography, or computed tomography), or detection of HCC via one imaging diagnostic modality and with a serum a-fetoprotein level of 400 ng/mL or greater.

Measures of Interaction

To test the null hypothesis, we performed a comprehensive assessment of interaction using relative excess risk caused by interaction (RERI), attributable proportion (AP) caused by interaction, and Rothman's synergy index (SI) and their 95% confidence interval (CI).[25] RERI is an estimate of excess risk that is attributable to the interaction between 2 exposures: family history of HCC and HBV status in this case. AP is defined as the proportion of risk that is attributable to the interaction. SI is a ratio that estimates whether a synergistic (SI, >1) or antagonistic (SI, <1) interaction exists between 2 exposures.[26,27]

Statistical Analysis

Person-years of follow-up evaluation for each participant were calculated as the time from study enrollment until the date of HCC diagnosis, the date of death, or December 31, 2008, whichever came first. Ididuals who were not diagnosed with HCC by death or by the last follow-up date were censored. The Kaplan–Meier curve was used to examine and estimate the cumulative incidence of HCC, and survival curves were compared using the log-rank test. Univariate and multivariate-adjusted hazard ratios (HRs) (with 95% CIs) of HCC were calculated using the Cox proportional hazards model. Significance levels were set at a P value of less than .05, and all statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Results

Baseline Characteristics

The study included 22,472 participants (50% women) who were followed up for a mean of 16.12 years (SD, 2.89 y). The mean age and body mass index was 47.2 years (SD, $\pm$ 10 y) and 24 kg/m^2 (SD, $\pm$ 3.4 kg/m^2), respectively. The prevalence of HBsAg was 17.5%, and among HBsAg-positive individuals 15.5% were HBeAg-positive. Family history of HCC was present in 2.4% of the entire cohort. Baseline characteristics of the cohort stratified by family history of HCC (yes or no) and presence (or absence) of HBsAg status are shown in Table 1.

Risk of Hepatocellular Carcinoma

There were a total of 374 HCC cases over 362,268 person-years of follow-up evaluation (Table 2). The cumulative rates of HCC in the 4 exposure categories including family history of HCC-negative and HBsAg-negative, family history of HCC-positive and HBsAg-negative, family history of HCC-negative and HBsAg-positive, and family history of HCC-positive and HBsAg-positive were 0.62%, 0.65%, 7.5%, and 15.8% ($P < .001$), respectively (Figure 1A).

Joint Effects of Family History of Hepatocellular Carcinoma and Hepatitis B Surface Antigen on Incident Hepatocellular Carcinoma Risk

Combined effects of family history of HCC and HBsAg showed a statistically significant and synergistic association with HCC risk, with the highest risk among those who had both a positive family history of HCC and HBsAg positivity in both unadjusted (HR, 28.33; 95% CI, 18.40–43.62; $P < .001$; Table 2) and multivariate-adjusted analyses (HR, 32.33; 95% CI, 20.78–50.30; $P < .01$), as shown in Table 3.

Assessment of Interaction Between Family History of Hepatocellular Carcinoma and Hepatitis B Surface Antigen

We then examined the RERI, AP, and SI; measures of synergistic interaction between family history of HCC (positive or negative) and HBsAg (positive or negative) in their association with incident HCC risk. We found that the RERI, AP, and SI were 19 (95% CI, 5.56–32.43), 0.59 (95% CI, 0.18–0.99), and 2.54 (95% CI, 1.62–3.99), respectively. These

findings suggest a synergistic interaction between family history of HCC and HBsAg in their joint association in increasing HCC risk.

Sensitivity Analyses

We further assessed the association between family history of HCC and the stage of HBV infection by performing subgroup analyses in patients who were HBsAg positive. Previous studies from the REVEAL cohort have shown that the presence of HBeAg and high HBV DNA level, defined as 10,000 copies/mL or greater, are both associated with increased risk of HCC.

Family History of Hepatocellular Carcinoma and Hepatitis B Virus DNA Levels in Hepatitis B Surface Antigen–Positive Patients

Combined effects of family history of HCC and HBV DNA showed a statistically significant and synergistic association with HCC risk, with the highest risk among those who had both a positive family history of HCC and high HBV DNA levels (10,000 copies/mL) in both unadjusted (HR, 13.75; 95% CI, 8.05–23.47; $P < .001$) and multivariate-adjusted analyses (HR, 15.72; 95% CI, 9.06–27.27; $P < .01$) (Supplementary Tables 1 and 2).

We then examined the RERI, AP, and SI between family history of HCC (positive or negative) and HBV DNA levels (10,000 or <10,000 copies/mL) in their association with incident HCC risk and found that the RERI, AP, and SI were 8.79 (95% CI, 0.89–16.69), 0.56 (95% CI, 0.18–0.93), and 2.48 (95% CI, 1.33–4.64), respectively, showing statistically significant synergistic interaction.

Family History of Hepatocellular Carcinoma and Hepatitis B e Antigen in Hepatitis B Surface Antigen–Positive Patients

Combined effects of family history of HCC and HBeAg showed a statistically significant and synergistic association with HCC risk, with the highest risk among those who had both a positive family history of HCC and were HBeAg positive in both unadjusted (HR, 10.86; 95% CI, 6.01–19.62; $P < .001$) and multivariate-adjusted analyses (HR, 20.14; 95% CI, 10.71–37.87; $P < .01$) (Supplementary Tables 3 and 4).

We then examined the RERI, AP, and SI between family history of HCC (positive or negative) and HBeAg (positive or negative) in their association with incident HCC risk and found that the RERI, AP, and SI were 12.87 (95% CI, 0.44–25.29), 0.64 (95% CI, 0.37–0.91), and 3.05 (95% CI, 1.53–6.10), respectively, showing statistically significant synergistic interaction.

Assessing the Effect of Family History of Hepatocellular Carcinoma, and Stages of Hepatitis B Virus Infection: Hepatitis B Surface Antigen–Positive, High or Low Hepatitis B Virus DNA Level, and Presence or Absence of Hepatitis B e Antigen

When analyses were stratified by family history of HCC (yes/no), and HBsAg (yes/no), HBeAg-negative status with or without high HBV DNA level (>10,000 copies/mL), and HBeAg-positive status, the risk of incident HCC synergistically increased dose-dependently in those with a positive family history of HCC across all stages of HBV infection, and was

highest in those with a family history of HCC and HBeAg positivity in multivariate-adjusted analyses (HR, 174.61; 95% CI, 92.2–330.8; $P < .01$), as shown in Table 4. The effect of the presence of family history of HCC remained significant and synergistic in each stage of HBV infection and multiplied the risk several-fold in those who already were at high risk for HCC (Table 4). Figure 1*B* shows that the presence of both a positive family history and HBeAg positivity increased the cumulative risk of HCC to 40%, underscoring clinical significance of these statistically significant results.

Association Between Risk of Hepatocellular Carcinoma and Number of Hepatocellular Carcinoma Cases Among First-Degree Relatives

Although there were trends suggesting that familial aggregation of HCC increased the risk of HCC, they were not significant in this cohort (Tables 5 and 6).

Discussion

Main Findings

In this large, well-characterized, prospective, community-dwelling cohort study, we showed that family history of HCC and HBsAg synergistically increases the risk of incident HCC among Taiwanese men and women. Family history of HCC multiplies the risk of HCC at each stage of HBV infection. Because family history of HCC effect modification of HCC risk in each stage of HBV infection was statistically significant and clinically meaningful, we therefore speculate that this suggests a significant shared host gene effect as the underlying mechanistic pathway to explain these findings. Future studies are warranted to examine whether more intensive HCC surveillance strategies should be considered in highest-risk HBV patients based on family history status similar to colon cancer.

By using RERI, AP, and SI, we showed that the interaction between family history of HCC and HBsAg is synergistic. Furthermore, we report that the risk approaches 40% when both family history of HCC and HBeAg are positive. These findings underscore the need for routine use of family history of HCC in risk assessment of patients with HBV for their HCC risk.[28] These data would form the basis for considering more stringent surveillance studies in these high-risk groups of patients with HBV. Future studies are needed to confirm whether the effect of family history of HCC on increasing the HCC risk in HBV patients is caused by shared gene effects or, perhaps, shared environment.[29]

Strengths and Limitations

Strengths of this study included a large prospective cohort comprising 24,272 participants who were followed up during 16 years, family history of HCC that was ascertained using a standardized questionnaire that was given to all the participants and obtained by self-report, and availability of potential confounders or effect modifiers as well as key HBV markers (such as HBsAg, HBeAg, and HBV DNA levels) associated with HCC at baseline for adjustment in the multivariate analyses. However, we acknowledge the following limitations of this study, including that the study population was exclusively Taiwanese. We did not have information on the age at diagnosis of HCC in family members, age at HBV infection in cases, and presence of family history of cirrhosis or HBV infection status in family

members. We did not adjust for delta hepatitis and anti–hepatitis B core antibodies in this study. However, we believe that these issues, although noteworthy, do not reflect a systematic bias that differentially favors the results in the opposite direction. Hence, these limitations are not likely to have influenced the study findings. Furthermore, the study was restricted to the association between family history of HCC and HBV infection, and these data are not general-izable to other liver diseases such as chronic hepatitis C infection, primary biliary cirrhosis, or nonalcoholic fatty liver disease. Family history was ascertained by self-report, and there was a possibility of recall bias. However, given that family history was recorded at baseline and we followed up all participants for incident HCC, it is unlikely that cases were likely to report (recall) family history of HCC, as is likely to happen in a case-control study.[29] Previous studies have shown that family history of cancer in first-degree relatives is likely to have 70% to 80% accuracy based on self-report.[30] Therefore, we included a positive family history in those who reported a first-degree relative with HCC.

In Context With Published Literature

Our results are consistent with previous reports showing that family history of HCC is an important risk factor for HCC.[16,31–33] Turati et al[18] conducted a case-control study (229 HCC patients vs 431 controls) and showed that the odds ratio of HCC was significantly higher in patients who had a family history of HCC and viral hepatitis B or C. They did not find a multiplicative interaction in their study. However, they did not examine RERI, AP, and SI to assess interaction. A basal core promoter mutation was associated with increased risk of HCC. However, the presence of a precore mutation was associated with a reduced risk of HCC. Neither of these factors showed a significant effect on modification of HCC risk with family history status. Our study used a large, prospective cohort design and assessed incident risk of HCC using Cox proportional hazards analyses and examined the presence of interaction using validated tools such as RERI, AP, and SI.[26] Therefore, our results provide robust prospective data and a comprehensive interaction assessment that will inform future research in this area.

Impact on Clinical Practice

Routine use of family history of HCC can further improve the HCC risk stratification of patients with hepatitis B. The cumulative risk of HCC when both family history and HBeAg are present is 40%. These patients should be considered at extremely high risk and more stringent screening and surveillance of HCC may be considered in this subset of patients because management of HCC is improving with transplantation, locoregional therapies, as well as newer chemo-therapeutic agents.[6,24] High-risk HCC subgroups may be identified in emerging centers of excellence in HCC care that may lead to early identification and prompt institution of therapies to manage HCC and improve morbidity and mortality caused by HCC.

Future Research Directions

Familial risk has been used in other cancers to perform earlier screening and surveillance such as in breast and colon carcinoma. Improved understanding of mechanisms underlying synergism between familial risk and HBV may refine prognostication for HCC risk and may lead to earlier and more stringent screening and surveillance strategies.[34] We challenge the

paradigm that family history does not have an interaction with HBV status and propose a multiplicative effect of family history and HBV on HCC risk. Further research is needed in a multi-ethnic population with and without viral hepatitis to assess whether this synergism is appreciated in diverse cohorts. Finally, more research is needed regarding whether anti-HBV therapies can reduce the risk of HCC in this subset of patients, especially those who have a family history of HCC.

Conclusions

By using a prospective cohort study design, we showed that family history of HCC multiplies the risk of HCC in patients with hepatitis B. This risk dose-dependently multiplied by the presence of HBeAg and higher levels of HBV DNA. Antiviral therapy should be considered in patients who are at highest risk of HCC such as those who have a family history of HCC, are HBeAg positive, and have an increased ALT level. Future studies are warranted to examine whether more intensive HCC surveillance strategies should be considered in highest-risk HBV patients based on family history status similar to other cancers such as colon cancer. We propose that shared gene effects along with shared environment,[29] albeit a lesser contribution, increases susceptibility to HCC. Exact underlying mechanisms remain to be elucidated. Whether screening and surveillance guidelines for HCC need to be revised based on familial risk and HBV status remains to be investigated in future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Abbreviations used in this paper

AP	attributable proportion
CI	confidence interval
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma

HR	hazard ratio
RERI	relative excess risk caused by interaction
REVEAL	Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus
SI	synergy index

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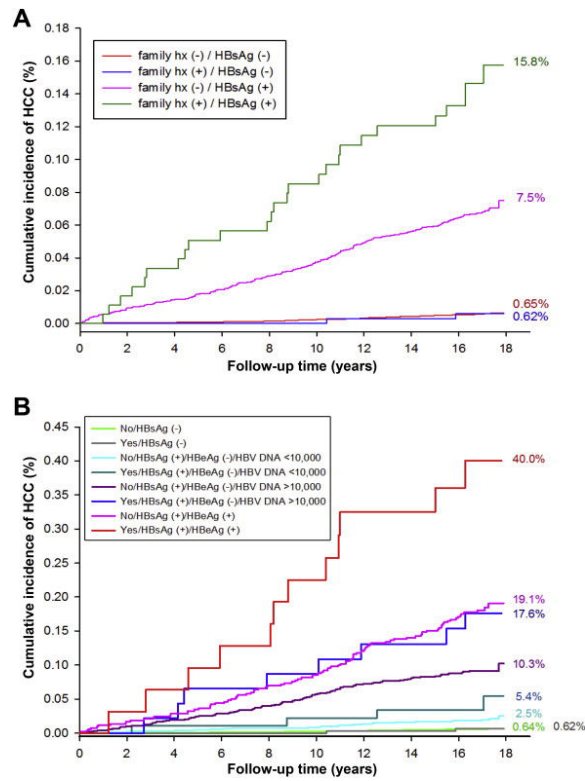
Figure 1.
(*A*) Family history of HCC, HBsAg serostatus, and risk of incident HCC. (*B*) Family history of HCC, HBsAg and HBeAg serostatus, HBV DNA level, and risk of incident HCC.

Table 1

Baseline Characteristics of the Cohort Stratified by the Family History of HCC and HBsAg

Characteristics	All	Subgroup			
		Family history of HCC negative and HBsAg negative	Family history of HCC positive and HBsAg negative	Family history of HCC negative and HBsAg positive	Family history of HCC positive and HBsAg positive
N	22,472	18,194	347	3751	180
HCC cases, n	374	100	2	246	26
Mean age ± SD, *y*	47.2 ± 10.0	47.5 ± 10.1	45.5 ± 9.4	45.9 ± 9.8	45.4 ± 9.2
Mean BMI ± SD, *kg/m²* [a]	24.0 ± 3.4	24.0 ± 3.4	24.0 ± 3.5	24.0 ± 3.4	23.7 ± 3.3
Alcohol use, n (%)[b]					
No	19,999 (89.2)	16,242 (89.5)	302 (87.0)	3298 (88.1)	157 (87.7)
Yes	2422 (10.8)	1908 (10.5)	45 (13.0)	447 (11.9)	22 (12.3)
Smoking, n (%)[c]					
No	15,917 (71.0)	13,025 (71.7)	245 (70.6)	2528 (67.5)	119 (66.1)
Yes	6517 (29.1)	5134 (28.3)	102 (29.4)	1220 (32.6)	61 (33.9)
ALT level, *U/L*					
<45	21,859 (97.3)	17,815 (97.9)	339 (97.7)	3537 (94.3)	168 (93.3)
45	613 (2.7)	379 (2.1)	8 (2.3)	214 (5.7)	12 (6.7)
Diabetes[d]					
No	21,867 (97.6)	17,693 (97.5)	341 (98.3)	3657 (97.7)	176 (97.8)
Yes	545 (2.4)	448 (2.5)	6 (1.7)	87 (2.3)	4 (2.2)
Genotype					
B	1923 (66.5)	N/A	N/A	1844 (66.9)	79 (57.7)
BC and C	970 (33.5)			912 (33.1)	58 (42.3)
Precore mutant (1896 G/A)					
Wild type	703 (38.2)	N/A	N/A	672 (38.3)	31 (35.6)
Mutant + mixed type	1138 (61.8)			1082 (61.7)	56 (64.4)
BCP mutant (1762/1764)					
Wild type	1031 (56.9)	N/A	N/A	990 (57.3)	41 (48.8)
Mutant + mixed type	782 (43.1)			739 (42.7)	43 (51.2)
HBeAg					
Seronegative	3155 (84.5)	N/A	N/A	3014 (84.7)	141 (81.5)
Seropositive	577 (15.5)			545 (15.3)	32 (18.5)
HBV DNA level, *copies/mL*					
HBV DNA level, <10,000	2035 (55.7)	N/A	N/A	1941 (55.7)	94 (54.7)
HBV DNA level, 10,000	1621 (44.3)			1543 (44.3)	78 (45.4)

ALT, alanine aminotransferase; BCP, basal core promoter mutation; BMI, body mass index.

[a] Fifty-three subjects were excluded because of missing data on body mass index.

[b] Fifty-one subjects were excluded because of missing data on alcohol use.

[c] Thirty-eight subjects were missing data on smoking.

[d]Sixty subjects were missing data on history of diabetes.

Table 2

Unadjusted and Multivariate Adjusted HRs for Incident HCC

Characteristic	N	HCC cases, n	Person-years of follow-up evaluation	Incidence rate per 100,000 person-years	Crude HR (95% CI)	Multivariate-adjusted HR (95% CI)
Age, *y*					1.06 (1.05-1.08)	1.08 (1.07-1.09)
BMI, *kg/m²*					1.05 (1.02-1.08)	1.04 (1.01-1.07)
Sex						
Female	11,081	91	182,624.8	49.83	Referent	Referent
Male	11,391	283	179,643.5	157.53	3.18 (2.51-4.02)	2.09 (1.58-2.77)
Smoking habit						
No	15,917	207	260,559.5	79.44	Referent	Referent
Yes	6517	165	101,085.5	163.23	2.07 (1.68-2.54)	1.11 (0.87-1.42)
Alcohol consumption						
No	19,999	294	324,238.9	90.67	Referent	Referent
Yes	2422	78	37,222.8	209.55	2.32 (1.81-2.98)	1.46 (1.12-1.91)
Diabetes						
No	21,867	350	353,976.7	98.88	Referent	Referent
Yes	545	23	7329.5	313.80	1.12 (0.98-1.28)	1.19 (1.02-1.39)
ALT level, *U/L*						
45	21,859	321	353,039.6	90.93	Referent	Referent
>45	613	53	9228.7	574.30	6.32 (4.73-8.46)	3.66 (2.72-4.94)
Family history of HCC						
Negative	21,945	346	353,905.6	97.77	Referent	Referent
Positive	527	28	8362.7	334.82	3.42 (2.33-5.03)	1.29 (0.32-5.24)
HBsAg serostatus						
Negative	18,541	102	300,596.8	33.93	Referent	Referent
Positive	3931	272	61,671.5	441.05	13.01 (10.36-16.33)	13.04 (10.28-16.54)
Family history of HCC/ HBsAg						
No/HBsAg-negative	18,194	100	294,950.6	33.90	Referent	Not included
Yes/HBsAg-negative	347	2	5646.2	35.42	1.04 (0.26-4.22)	
No/HBsAg-positive	3751	246	58,954.9	417.27	12.32 (9.76-15.54)	
Yes/HBsAg-positive	180	26	2716.6	958.10	28.33 (18.40-43.62)	

ALT, alanine aminotransferase; BMI, body mass index.

Table 3

Crude and Multivariate-Adjusted HRs of Incident HCC

Characteristic	All (N = 22,472)			HBsAg negative (n = 18,541)	HBsAg positive (n = 3931)	HBsAg-positive subset (n = 1767)
	Crude HR (95% CI)	Age/sex-adjusted HR (95% CI)	Multivariate adjusted HR (95% CI)	Multivariate adjusted HR (95% CI)	Multivariate adjusted HR (95% CI)	Multivariate adjusted HR (95% CI)
Sex						
Female	Referent	Referent	Referent	Referent	Referent	Referent
Male	3.18 (2.51-4.02)	2.47 (1.95-3.13)	2.09 (1.58-2.77)	1.05 (0.61-1.80)	2.85 (2.01-4.04)	3.02 (1.99-4.58)
Age, y	1.06 (1.05-1.08)	1.08 (1.06-1.09)	1.08 (1.07-1.09)	1.09 (1.06-1.11)	1.08 (1.06-1.09)	1.09 (1.07-1.11)
BMI, kg/m^2	1.05 (1.02-1.08)		1.04 (1.01-1.07)	1.05 (0.99-1.11)	1.04 (1.00-1.08)	1.04 (1.00-1.09)
Smoking habit						
No	Referent		Referent	Referent	Referent	Referent
Yes	2.07 (1.68-2.54)		1.11 (0.87-1.42)	1.42 (0.83-2.45)	1.06 (0.81-1.38)	1.22 (0.88-1.71)
Alcohol consumption						
No	Referent		Referent	Referent	Referent	Referent
Yes	2.32 (1.81-2.98)		1.46 (1.12-1.91)	1.32 (0.75-2.34)	1.50 (1.11-2.04)	1.26 (0.86-1.84)
Diabetes						
No	Referent		Referent	Referent	Referent	Referent
Yes	1.12 (0.98-1.28)		1.19 (1.02-1.39)	1.20 (0.99-1.46)	1.17 (0.92-1.49)	1.08 (0.82-1.44)
ALT level, *U/L*						
45	Referent		Referent	Referent	Referent	Referent
>45	6.32 (4.73-8.46)		3.66 (2.72-4.94)	3.19 (1.46-6.95)	3.65 (2.64-5.05)	2.17 (1.48-3.18)
Genotype[a]						
B	Referent					Referent
BC and C	2.53 (1.95-3.28)					1.88 (1.37-2.60)
Precore mutant (1896 G/A)[a]						
Wild type	Referent					Referent
Mutant + mixed type	0.49 (0.37-0.65)					0.49 (0.36-0.67)
BCP mutant (1762/1764)[a]						
Wild type	Referent					Referent

Characteristic	All (N = 22,472)			HBsAg negative (n = 18,541)	HBsAg positive (n = 3931)	HBsAg-positive subset (n = 1767)
	Crude HR (95% CI)	Age/sex-adjusted HR (95% CI)	Multivariate adjusted HR (95% CI)	Multivariate adjusted HR (95% CI)	Multivariate adjusted HR (95% CI)	Multivariate adjusted HR (95% CI)
Mutant + mixed type	2.47 (1.83-3.32)					1.78 (1.29-2.45)
Family history of HCC/HBsAg						
No/HBsAg negative	Referent	Referent	Referent	Referent		
Yes/HBsAg negative	1.04 (0.26-4.22)	1.26 (0.31-5.09)	1.29 (0.32-5.24)	1.26 (0.31-5.14)		
No/HBsAg positive	12.32 (9.76-15.54)	13.38 (10.59-16.91)	13.04 (10.28-16.54)		Referent	Referent
Yes/HBsAg positive	28.33 (18.40-43.62)	32.79 (21.26-50.58)	32.33 (20.78-50.30)		2.46 (1.63-3.72)	2.33 (1.40-3.88)

ALT, alanine aminotransferase; BCP, basal core promoter mutation; BMI, body mass index.

[a] Fifty-three subjects were excluded because of missing data on body mass index.

Table 4

Multivariate-Adjusted HRs of HCC by Family History Status and the Stage of HBV Infection Including HBsAg, HBeAg, and HBV DNA Level

Characteristic	Age/sex-adjusted HR (95% CI)	All (N = 22,472)	HBsAg positive only (n = 3931)
		Multivariate adjusted HR (95% CI)	Multivariate adjusted HR (95% CI)
Sex, male vs female	2.16 (1.69-2.75)	1.78 (1.33-2.39)	2.36 (1.63-3.41)
Age, *y*	1.09 (1.08-1.11)	1.09 (1.08-1.11)	1.10 (1.09-1.11)
BMI, *kg/m²*		1.05 (1.01-1.08)	1.05 (1.01-1.09)
Smoking habit, yes vs no		1.25 (0.97- 1.61)	1.24 (0.93-1.65)
Alcohol consumption, yes vs no		1.40 (1.06-1.86)	1.41 (1.03-1.94)
Diabetes, yes vs no		1.12 (0.96-1.31)	1.06 (0.83-1.36)
ALT level, >45 vs 45 U/L		2.23 (1.62-3.06)	2.04 (1.45-2.89)
Family history of HCC/HBsAg/HBeAG/HBV DNA level			
No/HBsAg negative	Referent	Referent	N/A
Yes/HBsAg negative	1.30 (0.32-5.26)	1.31 (0.32-5.33)	N/A
No/HBsAg positive/HBeAg negative/HBV DNA <10,000 copies/mL	3.75 (2.57-5.47)	3.87 (2.65-5.65)	Referent
Yes/HBsAg positive/HBeAg negative/HBV DNA <10,000 copies/mL	9.27 (3.41-25.20)	9.42 (3.46-25.63)	2.44 (0.87-6.84)
No/HBsAg positive/HBeAg negative/HBV DNA 10,000 copies/mL	17.22 (12.94-22.91)	17.37 (13.02-23.18)	4.43 (3.02-6.50)
Yes/HBsAg positive/HBeAg negative/HBV DNA 10,000 copies/mL	36.62 (17.80-75.35)	39.04 (18.91-80.61)	9.90 (4.59-21.37)
No/HBsAg positive/HBeAg positive	60.21 (44.79-80.95)	52.33 (38.36-71.37)	13.91 (9.31-20.77)
Yes/HBsAg positive/HBeAg positive	178.38 (96.83-328.63)	174.61 (92.16-330.83)	45.52 (22.86-90.63)

NOTE. We did not adjust for genotype and mutants because these data were available only in patients with a DNA level greater than 10,000.

ALT, alanine aminotransferase; BMI, body mass index.

Table 5

Multivariate-Adjusted HRs of HCC According to the Number of First-Degree Relatives With HCC

Characteristic	All with positive family history (N = 527)	HBsAg positive only (N = 180)
	Age/sex-adjusted HR (95% CI)	Multivariate adjusted HR (95% CI)
Sex, male vs female	2.40 (0.86-6.68)	1.81 (0.56-5.88)
Age, *y*	1.05 (1.01-1.10)	1.06 (1.02-1.10)
BMI, *kg/m^2*	0.98 (0.88-1.10)	0.97 (0.84-1.12)
Smoking habit, yes vs no	1.26 (0.49-3.25)	1.76 (0.65-4.74)
Alcohol consumption, yes vs no	0.62 (0.17-2.20)	0.78 (0.21-2.94)
Diabetes, yes vs no	1.79 (0.24- 13.59)	1.44 (0.18-11.80)
ALT level, >45 vs 45 U/L	9.16 (3.53-23.76)	6.71 (2.36-19.02)
First-degree relatives with HCC, n		
1	1.0	1.0
1	1.83 (0.53-6.32)	1.57 (0.43-5.72)

NOTE. We could not look at genotype or mutant data because there were no data for more than 80% of these individuals because the majority of people were HBsAg negative. There were only 2 HCC cases among HBsAg-negative participants, so it was not possible to perform this analyses in this subset.

ALT, alanine aminotransferase; BMI, body mass index.

Table 6

Distribution of HCC Cases and Number of Relatives With HCC

Characteristic	HCC non-case	HCC case
1 first-degree relative with HCC	465	25
1 first-degree relative with HCC	34	3