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Increased risk for hepatitis B-related liver cirrhosis in relatives of patients with hepatocellular carcinoma in northern Taiwan

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Background There is a tendency for familial aggregation of hepatocellular carcinoma (HCC). The aims of this study were to assess the degree to which familial aggregation of hepatitis B surface antigen (HBsAg) carriers accounts for familiality of HCC in families of hepatitis B-related HCC patients, and whether HCC shares a familial predisposition with liver cirrhosis among HBsAg carriers.

Methods A total of 671 first-degree relatives of HBsAg-positive HCC cases were recruited using abdominal ultrasonography and tests for HBsAg and serum aminotransferases. They were from 165 simplex families defined as having only one HCC case and 72 multiplex families with more than one case. In analyses of family history of HCC and cirrhosis, the data set consisted of 4471 unrelated asymptomatic HBsAg carriers recruited in a prospective study.

Results There was no significant difference in the HBsAg-positive rate among relatives between multiplex (55.7%) and simplex (48.1%) families. Sonographic evidence of liver cirrhosis was present in 14.4% of HBsAg-positive relatives from multiplex families but in only 7.8% of HBsAg-positive relatives from simplex families (multiplex versus simplex families: adjusted odds ratio [OR] = 2.29; 95% CI: 1.10–4.77). Among unrelated asymptomatic HBsAg carriers, the adjusted OR of liver cirrhosis associated with a first-degree family history of HCC was 2.80 (95% CI: 1.68–4.66). This association was stronger in HBsAg carriers <50 years. No association was seen between family history of HCC and hepatitis activity based on elevated levels of aminotransferases.

Conclusions Familial aggregation of HCC in HBsAg carriers is associated with familial clustering of liver cirrhosis.

Keywords Hepatitis B, liver cirrhosis, hepatocellular carcinoma, familial aggregation

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It has been demonstrated that first-degree relatives of hepatitis B surface antigen (HBsAg) carriers with hepatocellular carcinoma (HCC) have an increased risk of HCC as compared with the same relatives of HBsAg carriers without HCC.[1] However, the cause for this familial clustering of HCC remains unclear.

Many possible aetiological factors have been implicated in the development of HCC, but most of these such as alcohol, aflatoxins, gender, tobacco smoke, and certain polymorphic genes increase only a relatively modest risk of HCC.[2–11] Most HCC has been associated with hepatitis virus infections.[11] In Taiwan, where mother-to-child vertical transmission is the predominant route of acquiring chronic hepatitis B virus (HBV) infection,[12] HBV is the major cause of HCC and the important source of familial effects for HCC.[11] The risk of developing HCC among HBsAg carriers is closely related to hepatitis activity and

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advanced stage of liver disease.[13,14] Although the HCC risk is extremely high for HBsAg carriers as compared with non-carriers,[11] most HBsAg carriers may have no clinical symptoms of liver disease and no or only minor histological lesions in the liver through their lifetime. Indeed, only a small fraction of HBsAg carriers develop advanced chronic liver disease, such as chronic hepatitis and liver cirrhosis, which are closely associated with the development of HCC.[15–17] The cirrhosis caused by persistent HBV infection often progresses insidiously. The usefulness of ultrasonography in the diagnosis of cirrhosis in patients with chronic hepatitis B has been established.[16,18,19] Our previous prospective study found that subclinical cirrhosis diagnosed by ultrasonography is the most influential known risk factor for the development of HCC among HBsAg carriers, conferring an increased relative risk of about 12.[17]

This study was based on data from a cohort study of asymptomatic HBsAg carriers and a family study in which information regarding most potentially relevant risk factors for HCC was collected from relatives of patients with HBV-related HCC. It aimed both to assess the extent to which familial aggregation of HBsAg carriers could account for familial clustering of HCC in families of hepatitis B-related HCC patients, and to investigate whether HCC shares a familial predisposition with other liver diseases, especially cirrhosis, among HBsAg carriers.

Subjects and Methods

The study population consisted of relatives of patients with HCC who participated in an ongoing family study of HCC and a cohort of unrelated asymptomatic HBsAg carriers enrolled in a prospective study on HCC, which has been in operation since 1988 (Figure 1).

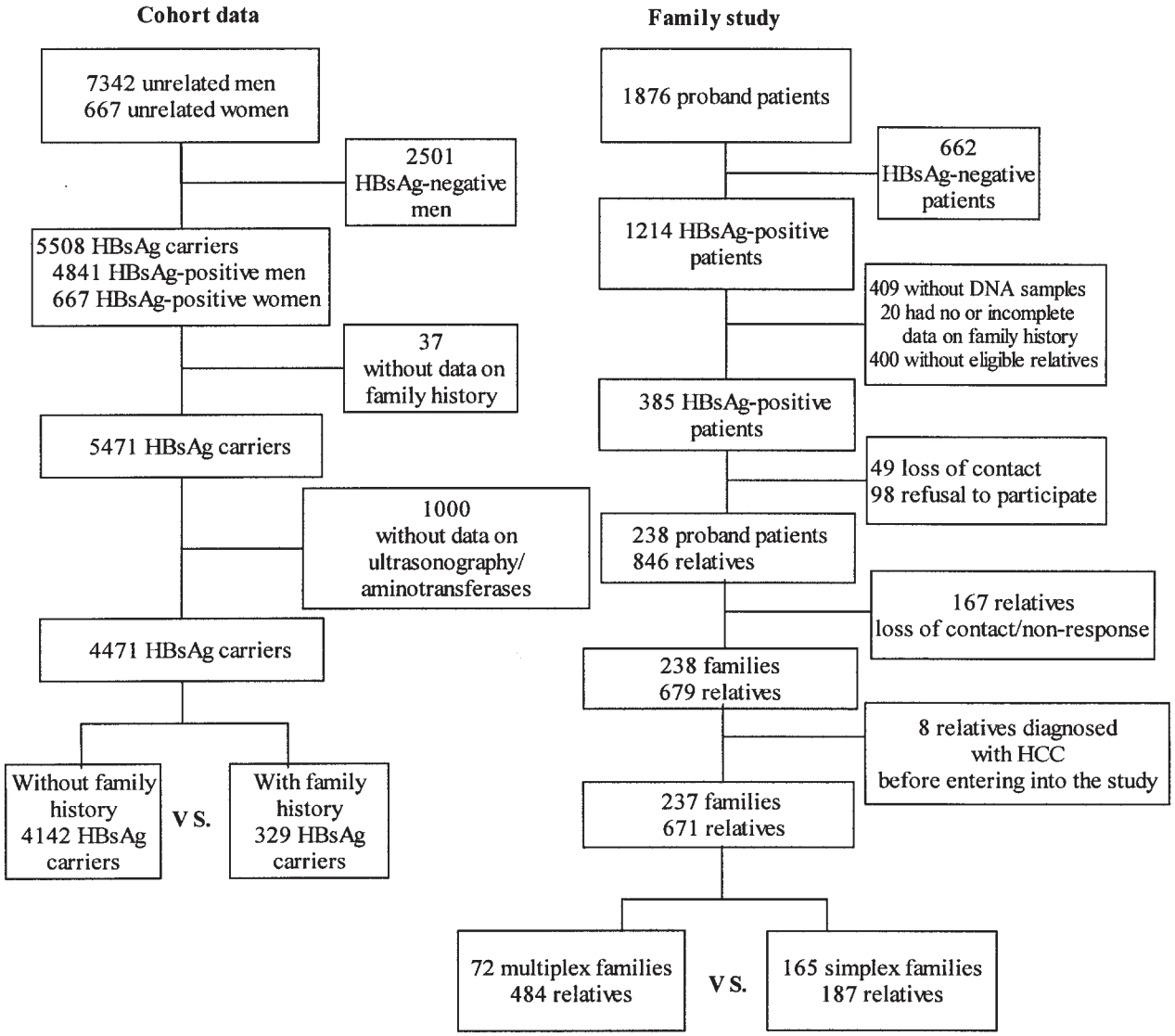

Figure 1 Flowchart of study design and recruitment of study subjects

Family study

Between September 1997 and May 2000 a total of 1876 (1214 of whom were HBsAg-positive) patients with HCC diagnosed on the basis of histological findings or an elevated serum α-fetoprotein level (≥400 ng/ml) combined with at least one positive image on angiography, sonography, and/or computed tomography were enrolled with family history interview and/or blood collection from four major hospitals in northern Taiwan.

Recruitment of study families was initiated in August 1998. For the purpose of genetic linkage analysis, only families of HCC patients for whom DNA samples were available were considered. Names and telephone numbers of relatives were obtained from the HCC index case and/or family members. Relatives were eligible for inclusion if they were aged 20–75 years and residing in Taipei City or districts near Taipei. Surviving siblings and parents of all HBsAg-positive HCC patients and of HBsAg-negative HCC patients diagnosed with cancer before 45 years of age were asked to come to our research centre for clinical evaluation, including ultrasound scanning and tests for serum levels of aminotransferases and HBsAg. Because the average age at onset of HCC in Taiwan is about 50 years, children of the index patient were invited to participate in this study if their HBsAg status was known on the index patient's family history questionnaire and they were tested positive for HBsAg. Since the report of physical examination including items of serological markers for hepatitis B is required for students to attend certain universities in Taiwan, many parents know whether their adult children are positive for HBsAg. Status of liver cirrhosis was determined on the basis of ultrasonographic patterns characteristic of cirrhosis as described previously.[17] Ultrasonography was performed by gastroenterologists who had no prior knowledge of the family history of HCC. Hepatitis B surface antigen was detected by enzyme immunoassay (SURASE B-96, General Biologicals Corporation, Hsinchu, Taiwan). Each relative was also asked to complete a structured questionnaire including items on sociodemographic factors, lifestyle habits, and a medical history. This study was approved by the research ethics committee at the College of Public Health, National Taiwan University and the appropriate institutional review board.

Only relatives of HBsAg-positive HCC patients were considered in the present analysis. Of 1214 HBsAg-positive patients with HCC, 409 had no DNA, 20 had no or incomplete data on family history of HCC and 400 (including 146 with no surviving eligible relatives, 74 whose parents and siblings were too old, and 180 whose relatives resided in areas far away from Taipei city) had no eligible relatives. Forty-nine patients' families could not be contacted and 98 declined to take part. The maximum possible number of eligible relatives of the 238 remaining patients' families was 846. A total of 80% (679 relatives) of them were recruited. We excluded eight relatives diagnosed with HCC before entry into the study. A total of 671 relatives (130 parents, 474 siblings, 67 children) from 237 families (including 72 multiplex families defined as having at least one HCC case among first-degree relatives of the index cases and 165 simplex families having no HCC cases among first-degree relatives of the index cases) remained available for analysis in this study. Of the 237 patients whose relatives were included as study subjects, 64% were diagnosed with HCC before age 50, whereas the corresponding figure for the 977 patients whose relatives were not included was 39%. Fifty-five per cent of the 237 patients had an education level of senior high school or above. However, only 38% of the 977 patients had such an education level. The average number of relatives who participated in this study in each family was 2.6 (range = 1–9) for multiplex families and 2.9 (range = 1–8) for simplex families.

Cohort data

The cohort consisted of 7342 men and 667 women in which male HBsAg carriers and/or non-carriers had been included in our previous studies to examine various hypotheses for the origin of HCC.[1,4–10] A total of 4471 HBsAg carriers (4025 men and 446 women) were included in the present study.

A detailed description of the enrolment and follow-up of HBsAg carriers in this cohort study has been published elsewhere.[1,4–10] Briefly, between 1988 and 1992, asymptomatic HBsAg carriers who were free of diagnosed HCC were consecutively enrolled during routine physical examinations from the Government Employee Central Clinics and the Liver Unit of Chang-Gung Memorial Hospital. All participants gave their written informed consent. Details of their sociodemographic characteristics, lifestyle habits, as well as personal and family medical histories were collected using standardized questionnaires by trained research assistants. Blood specimens were also obtained and frozen at –70°C until subsequent analysis.

Hepatitis B surface antigen carriers were periodically evaluated by medical examination including tests for serum alanine aminotransferase, aspartate aminotransferase, and α-fetoprotein levels. Ultrasonography was performed routinely for the detection of cirrhosis and HCC. The data collected at the initial examination were used in this study. Of the original 5508 HBsAg carriers in the cohort, 37 (0.7%) had no available data on family history of HCC and 1000 (18.2%) had no data on either ultrasonography measurement or serum aminotransferases, leaving a total of 4471 HBsAg carriers in the analysis.

Statistical analysis

We used the χ^2 test to compare groups for categorical variables. Odds ratios (OR) comparing disease risks between relatives from multiplex and simplex families were estimated by a logit marginal model taking account of within-family dependence.[20] The models were fitted by use of the GENMOD procedure of the statistical package PC-SAS version 6.12. We estimated the standard errors of the OR by use of the exchangeable working correlation matrix. When risks associated with family history of HCC among unrelated cohort HBsAg carriers were analysed, an unconditional logistic model was used instead to compute OR and their 95% CI. Multivariate models were adjusted for age (continuous variable), sex, cigarette smoking (yes or no), alcohol consumption (yes or no), and years of education (continuous variable). All *P*-values presented are two-sided.

Results

Parents and siblings of HCC patients from multiplex families (55.7%) had a slightly higher HBsAg-positive rate than those from the simplex families (48.1%). However, the difference by family history of HCC was not statistically significant even after adjusting for age, sex, and the relationship of the relative with the index case (mother, father, or siblings) in a logistic regression

model taking account of within-family dependence. Children were not included for this comparison because they were recruited with knowledge of HBsAg status (Table 1).

Among the 4471 cohort HBsAg carriers, 329 (7.4%) reported a first-degree relative with HCC. Only 22 of the cohort subjects with such a family history had more than one first-degree relative with HCC. Table 2 shows characteristics in HBsAg carriers by source of recruitment and family history of HCC. Among cohort subjects, HBsAg carriers with a first-degree family history of HCC were somewhat younger than those without ($P = 0.029$). Otherwise, cohort HBsAg carriers with and without a first-degree family history of HCC had similar distributions of gender, alcohol consumption and cigarette smoking habits, and educational levels. None of the distributions of the selected

Table 1 Hepatitis B surface antigen (HBsAg)-positive rate in parents and siblings of patients with hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC) by types of families[a]

				HBsAg positivity	
Family type	**No. of family**	**Relation to HCC index case**	**No. of relatives tested**	No.	(%)
Simplex	161	Parents	116	43	(37.1)[b]
		Siblings	348	180	(51.7)[c]
		All	464	223	(48.1)[d]
Multiplex	60	Parents	14	6	(42.9)
		Siblings	126	72	(57.1)
		All	140	78	(55.7)

[a] Multiplex family was defined as a family containing at least one HCC case among first-degree relatives of the HCC index case. Children were not included for this comparison because they were recruited with knowledge of HBsAg status.

[b] $P = 0.673$ for the comparison with multiplex families.

[c] $P = 0.296$ for the comparison with multiplex families.

[d] $P = 0.128$ for the comparison with multiplex families.

Table 2 Characteristics of hepatitis B surface antigen (HBsAg) carriers by source of recruitment and a first-degree family history of hepatocellular carcinoma (HCC)

	Cohort HBsAg carriers		**HCC patients' HBsAg-positive first-degree relatives[a]**	
Characteristic	Without family history, % ($n = 4142$)	With family history, % ($n = 329$)	Simplex families, % ($n = 243$)	Multiplex families,[b] % ($n = 125$)
Age (years)				
<30	1.2[c]	1.5	9.9	16.8
30–39	30.5	30.7	25.5	25.6
40–49	39.2	45.3	38.3	36.0
50–59	18.0	16.4	12.7	12.8
≥60	11.1	6.1	13.6	8.8
Female	9.9	11.6	55.1	54.4
Years of education[d]				
≤9	20.7	25.6	37.9	37.4
10–12	21.4	18.9	33.7	36.6
>12	57.9	55.5	28.4	26.0
Cigarette smoking				
Non-smokers	68.4	67.8	69.1	70.4
Ex-smokers	7.2	7.3	5.8	1.6
Current smokers	24.4	24.9	25.1	28.0
Frequency of alcohol consumption (days/week)				
Non-drinkers	81.9	80.5	85.2	83.2
1–3	14.2	15.2	10.7	12.0
4–7	3.8	4.3	4.1	4.0
Drinkers with unknown frequency	0.1	0.0	0.0	0.8

[a] Relatives included parents, siblings and children.

[b] Multiplex family was defined as a family containing at least one HCC case among first-degree relatives of the HCC index case.

[c] $P = 0.029$ for the comparison with cohort HBsAg carriers with a first-degree family history of HCC.

[d] Data on years of education were missing for four cohort subjects without a first-degree family history of HCC, one cohort subject with a first-degree family history of HCC, and two relatives of familial HCC patients.

characteristics in Table 2 significantly differ between relatives from multiplex families and relatives from simplex families.

Among HBsAg carriers, the prevalence of elevated aminotransferase levels (defined as alanine aminotransferase>40 IU/l or aspartate aminotransferase>35 IU/l) did not significantly differ between cohort HBsAg carriers with and without a first-degree family history of HCC, and between relatives of familial HCC patients defined as having at least one first-degree relative affected with HCC and those relatives of sporadic patients without affected first-degree relatives. However, there was an association between cirrhosis risk and family history of HCC among HBsAg carriers. The relatives (14.4%) of familial HCC patients were more likely to have ultrasonographic evidence of cirrhosis than the relatives (7.8%) of sporadic HCC patients (adjusted OR = 2.29; 95% CI: 1.10–4.77; $P = 0.0263$). Compared with cohort HBsAg carriers without a first-degree family history of HCC, the adjusted OR of having ultrasonographic evidence of cirrhosis for cohort HBsAg carriers with such a family history was 2.80 (95% CI: 1.68–4.66; $P = 0.0001$) (Table 3). Of the 303 HBsAg-negative parents and siblings of HCC index patients, only 30 (9.9%) had elevated aminotransferase levels and 3 (1.0%) were found to have cirrhosis by ultrasonography (data not shown).

The proportion of subjects who reported having a history of cirrhosis diagnosed by physicians was also significantly higher in cohort HBsAg carriers with a first-degree family history of HCC than in those without, although this proportion was lower in relatives of familial HCC patients than in relatives of sporadic patients. Relatives of patients with HCC may have greater diagnostic surveillance and those relatives who have had disease may have a higher participation rate. To evaluate possible distortion of our findings by this selection bias, we repeated our analysis after excluding subjects with a history of cirrhosis. As shown in Table 3, the association between ultrasonographic evidence of cirrhosis and family history of HCC remained significant even after exclusion of subjects who reported having a history of cirrhosis diagnosed by physicians.

Table 4 shows a higher prevalence of cirrhosis diagnosed by ultrasonography among older (≥50 years) than among younger HBsAg carriers. However, the association between family history of HCC and cirrhosis tended to be stronger in younger HBsAg carriers.

Discussion

It has long been observed that there is familial clustering of HCC and of chronic HBV infection.[21] Studies to elucidate hypothesized susceptibility to HCC thus must consider HBV. In a previous study we observed a profound familial effect for the development of HCC in the context of HBV exposure using a cohort study of 4808 HBsAg carriers and a case-control family study involving 553 HBsAg carriers with HCC and 4684 HBsAg carriers without HCC. No excess of other types of cancer was observed in the case families, but the prevalence of cirrhosis among first-degree relatives, in which information on cirrhosis was obtained from the case and control probands, was also found to be significantly greater for case subjects than for control subjects.[1] That study raises the possibility that there may be genetic factors or shared environmental exposure(s) other than chronic HBV infection contributing to the familial

Table 3 Odds ratios (OR) of elevated aminotransferase levels and cirrhosis according to a first-degree family history of hepatocellular carcinoma (HCC) among hepatitis B surface antigen (HBsAg) carriers by source of recruitment[a]

	Cohort HBsAg carriers		HCC patients' HBsAg-positive first-degree relatives[b]	
Diagnosis	Without family history ($n = 4142$)	With family history ($n = 329$)	Simplex families ($n = 243$)	Multiplex families[c] ($n = 125$)
Elevated aminotransferases				
Prevalence (%)	1150 (27.8)	95 (28.9)	58 (23.9)	35 (28.0)
Crude OR (95% CI)	1.0 (ref.)	1.06 (0.82–1.35)	1.0 (ref.)	1.28 (0.76–2.15)
Adjusted OR (95% CI)	1.0 (ref.)	1.02 (0.79–1.31)	1.0 (ref.)	1.26 (0.74–2.15)
Cirrhosis diagnosed by ultrasonography				
Prevalence (%)	105 (2.5)	19 (5.8)	19 (7.8)	18 (14.4)
Crude OR (95% CI)	1.0 (ref.)	2.36 (1.43–3.89)	1.0 (ref.)	1.98 (1.01–3.88)
Adjusted OR (95% CI)	1.0 (ref.)	2.80 (1.68–4.66)	1.0 (ref.)	2.29 (1.10–4.77)
History of cirrhosis				
Prevalence (%)	16 (0.4)	4 (1.2)	9 (3.7)	3 (2.4)
Crude OR (95% CI)	1.0 (ref.)	3.17 (1.06–9.55)	1.0 (ref.)	0.43 (0.09–2.04)
Adjusted OR (95% CI)	1.0 (ref.)	3.74 (1.22–11.52)	1.0 (ref.)	0.51 (0.11–2.41)
Cirrhosis diagnosed by ultrasonography, excluding subjects who reported having a history of cirrhosis[d]				
Prevalence (%)	98 (2.4)	15 (4.6)	13 (5.6)	16 (13.1)
Crude OR (95% CI)	1.0 (ref.)	1.99 (1.14–3.47)	1.0 (ref.)	2.55 (1.20–5.43)
Adjusted OR (95% CI)	1.0 (ref.)	2.34 (1.33–4.12)	1.0 (ref.)	3.11 (1.38–7.00)

[a] Multivariate-adjusted OR have been adjusted for age (continuous variable), sex, cigarette smoking (yes or no), alcohol consumption (yes or no), and years of education (continuous variable). Four cohort subjects without a first-degree family history of HCC, one cohort subject with a first-degree family history of HCC, and two relatives of familial HCC patients were not included in the multiple logistic regression analyses because of missing data on years of education.

[b] Relatives included parents, siblings and children.

[c] Multiplex family was defined as a family containing at least one HCC case among first-degree relatives of the HCC index case.

[d] Subjects who reported having a history of cirrhosis but were not detected with cirrhosis by ultrasonography were also excluded from the analyses.

Table 4 Odds ratios (OR) of having cirrhosis diagnosed by ultrasonography in relation to a first-degree family history of hepatocellular carcinoma (HCC) among hepatitis B surface antigen (HBsAg) carriers by source of recruitment and age[a]

	Cohort HBsAg carriers		**HCC patients' HBsAg-positive first-degree relatives[b]**	
Variable	Without family history (n = 4142)	With family history (n = 329)	Simplex families (n = 243)	Multiplex families[c] (n = 125)
<50 years of age				
No. with cirrhosis/total no.	44/2937	12/255	11/179	12/98
Crude OR (95% CI)	1.0 (ref.)	3.25 (1.69–6.23)	1.0 (ref.)	2.13 (0.90–5.05)
Adjusted OR (95% CI)	1.0 (ref.)	3.27 (1.69–6.32)	1.0 (ref.)	2.65 (0.99–7.12)
≥50 years of age				
No. with cirrhosis/total no.	61/1205	7/74	8/64	6/27
Crude OR (95% CI)	1.0 (ref.)	1.96 (0.86–4.45)	1.0 (ref.)	1.99 (0.63–6.32)
Adjusted OR (95% CI)	1.0 (ref.)	2.03 (0.89–4.64)	1.0 (ref.)	1.71 (0.49–5.97)

[a] Multivariate-adjusted OR have been adjusted for age (continuous variable), sex, cigarette smoking (yes or no), alcohol consumption (yes or no), and years of education (continuous variable). Four (2 aged ≥50 years and 2 aged <50 years) cohort subjects without a first-degree family history of HCC, 1 cohort subject aged <50 years who had a first-degree family history of HCC, and 2 (1 aged <50 years and 1 aged ≥50 years) relatives of familial HCC patients were not included in the multiple logistic regression analyses because of missing data on years of education.

[b] Relatives included parents, siblings and children.

[c] Multiplex family was defined as a family containing at least one HCC case among first-degree relatives of the HCC index case.

risk of HCC, perhaps the mechanism by which these factors cause familial HCC is through the process leading to cirrhosis. However, neither analysis in that study included data on HBsAg status of the relatives. Given the importance of HBsAg status for HCC risk, the role of chronic HBV infection in familial HCC merits more careful consideration.

This study, in which actual test data on the HBsAg status of the relatives were collected, maintains that HBV alone cannot explain all of the familial concordance of HCC, because the prevalence of HBsAg carrier rate in simplex and multiplex families of HCC was not significantly different. The reported increase in the risk of HCC has also been attributed to environmental risk factors other than HBV, particularly hepatitis C virus.[2–11,22] However, most seroepidemiological surveys on the prevalence of hepatitis C virus infection using first- or second-generation immunoassay kits to test antibodies against hepatitis C virus in selected populations in northern Taiwan have reported a prevalence of 0.3–2.5%,[22–24] except a study conducted in a specific township with high incidence of HCC, in which the figure was as high as about 10%.[25] Otherwise, although intrafamilial spread of hepatitis C virus may occur, the possibility of transmission of hepatitis C virus through non-sexual household contacts seems to be low.[26,27] Although we failed to observe an association with family history of HCC for hepatitis activity manifested by elevated aminotransferase levels in this study, the prevalence of cirrhosis diagnosed by ultrasonography was found to be associated with familiality of HCC among HBsAg carriers. This finding is compatible with that from our previous work[1] and suggests that the response to persistent infection with HBV, rather than its mere presence, may play a considerable role in the familial risk of HCC.

Despite intensive recruitment, some eligible relatives in HCC index patients' families that could be contacted refused to participate in this survey. It is conceivable that a preferential participation rate by affected compared to unaffected relatives could lead to an overestimation of the true prevalence of cirrhosis among relatives of patients with HCC. However, the cirrhosis caused by HBV often progresses insidiously. In contrast to the prevalence of cirrhosis diagnosed by ultrasonography, the proportion of subjects who reported having a history of cirrhosis diagnosed by physicians among HBsAg carriers is relatively low. Thus, it is reasonable to speculate that the participation rate in relatives affected by subclinical cirrhosis would be similar to that in those unaffected. On the other hand, relatives of HCC patients may receive excess ultrasonographic screening for early detection of HCC. The proportion of subjects who reported having a history of cirrhosis was also observed to be higher among cohort HBsAg carriers with a first-degree family history of HCC than among those without. However, the association between ultrasonographic evidence of cirrhosis and family history of HCC among cohort HBsAg carriers remained statistically significant even after excluding subjects who reported having a history of cirrhosis from analyses.

A limitation of our study is that a fraction of subclinical cirrhosis may not be diagnosed by ultrasonography, particularly for early liver cirrhosis.[18,19] Compared with liver biopsy, the specificity of ultrasonography in the diagnosis of cirrhosis was found to be very high. However, the limited sensitivity of the ultrasonographic diagnosis may have led to some underestimation of the relationship between cirrhosis and family history of HCC.

The reasons for the familial occurrence of cirrhosis remain unknown. It may be caused by prolonged HBV replication, which was also reported to cluster in first-degree relatives of patients with HCC.[28] Recently, various genotypes of HBV have been identified by a novel genotyping method based on analysis of the surface gene. Genotypes B and C are the predominant strains in Taiwan. Whereas genotype C was observed to be associated with cirrhosis, genotype B may be associated with the development of early-onset HCC.[29] It is possible that familial aggregation of cirrhosis in relatives of patients with HCC observed in this study may be related to the vertical transmission of particularly virulent strains of HBV. Nevertheless, the exact nature of the relationship between HBV genotypes and liver disease severity remains unclear.

In addition to the genetic variability of the virus, the course of persistent HBV infection may also depend on host genetic factors. Segregation analysis of HCC in Chinese families has demonstrated an HBV-major gene interaction.[30] In this study, we observed an approximately threefold increase in the cirrhosis risk for cohort HBsAg carriers with a first-degree family history of HCC compared with those HBsAg carriers without such a family history. Simulation studies have shown that a shared environmental factor, even if it is perfectly associated between relatives, is incapable of doubling disease risk in relatives of those affected compared with those unaffected, unless the factor induces a 10-fold or greater increase in risk for the disease.[31,32] Moreover, our previous case-control family study found that the risk of HCC in first-degree relatives tended to be higher among patients with early-onset HCC diagnosed at less than 50 years of age.[1] We also found that the association of cirrhosis with family history of HCC is stronger among HBsAg carriers <50 years in the present study. In addition, HBV carriers from multiplex families have a higher risk of cirrhosis than those from simplex families, suggesting the existence of a rare high-risk gene accounting for HBV-related cirrhosis. Mapping and molecular characterization of the inherited susceptibility to cirrhosis could contribute substantially to the understanding of familial HCC.

In summary, we found an association of cirrhosis risk with a family history of HCC in first-degree relatives among HBsAg carriers. This finding raises an important clinical and public health issue. Should HBsAg carriers with such a family history of HCC be treated more actively to prevent progress into cirrhosis? Treatments with lamivudine or interferone have been associated with sustained suppression of HBV replication and/or substantial histological improvement in certain HBsAg carriers.[33–36] However, follow-up studies are required to determine the effectiveness of such treatments in prevention of developing cirrhosis and HCC.

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KEY MESSAGES

- Chronic hepatitis B virus infection alone cannot explain all of the familial concordance of hepatocellular carcinoma (HCC).
- Familial aggregation of HCC in hepatitis B surface antigen (HBsAg) carriers is associated with familial clustering of liver cirrhosis.
- Prophylactic treatment to prevent liver cirrhosis should be considered for HBsAg-positive first-degree relatives of HCC patients.

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