

Familial Risk of Hepatocellular Carcinoma Among Chronic Hepatitis B Carriers and Their Relatives

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Background: Familial predisposition as a risk factor for hepatocellular carcinoma (HCC) in hepatitis B virus (HBV) carriers has not been thoroughly explored. **Methods:** The HCC risk associated with having parents and/or siblings with HCC was evaluated by use of a cohort study of 4808 male HBV carriers. A case-control family study was also conducted on data from first-degree relatives of 553 HBV carriers who had newly diagnosed HCC (case subjects) and 4684 HBV carriers without HCC (control subjects). **Results:** In the cohort study, HBV carriers with a family history of HCC had a multivariate-adjusted rate ratio for HCC of 2.41 (95% confidence interval [CI] = 1.47–3.95) compared with HBV carriers without a family history of HCC. For carriers with two or more affected relatives, the ratio increased to 5.55 (95% CI = 2.02–15.26). Cumulative HCC risk by age 70 years was 235.6 per 1000 (95% CI = 95.3–375.9 per 1000) for HBV carriers with family history compared with 88.9 per 1000 (95% CI = 67.9–109.9 per 1000) for those without. In the case-control family study, first-degree relatives of case subjects were more likely to have HCC (age-sex-adjusted odds ratio [OR] = 2.57; 95% CI = 2.03–3.25) than first-degree relatives of control subjects. The excess risk of HCC among relatives was particularly evident in siblings (sisters—age-adjusted OR = 4.55 [95% CI = 2.22–9.31]; brothers—age-adjusted OR = 3.73 [95% CI = 2.64–5.27]), but it was also observed in parents. The cumulative risk of HCC to age 80 years was 83.0 per 1000 among relatives of case subjects and 42.0 per 1000 among relatives of control subjects. Among rela-

tives of case subjects, the cumulative risk of HCC was greater if the case subjects were diagnosed before age 50 years (two-sided $P = .047$). Liver cirrhosis was 2.29 (95% CI = 1.68–3.11) times more frequent in relatives of case subjects than in relatives of control subjects. **Conclusions:** First-degree relatives of patients with HBV-related HCC appear to be at increased risk of HCC and should be considered in the formulation of HCC-screening programs. [J Natl Cancer Inst 2000;92:1159–64]

Hepatocellular carcinoma (HCC) ranks as one of the most common cancers in the world (1). The most clearly established risk factors for HCC are liver cirrhosis, chronic infection with hepatitis B and/or C viruses, aflatoxin exposure, male sex, alcohol drinking, and cigarette smoking (2–9). In Taiwan, where the incidence rate of HCC is among the highest in the world, chronic infection with hepatitis B virus (HBV) appears to account for at least 70% of HCC (2,4). The HCC risk is extremely high, with a relative risk of about 20, for chronic HBV carriers as compared with noncarriers (4). However, only a fraction of chronic HBV carriers are expected to develop HCC in their lifetime (2,5). Whereas most chronic HBV carriers in Taiwan are infected by HBV during their early childhood (10,11), they are affected by HCC in a wider range of ages of onset, ranging from less than 5 years old to more than 70 years old (2,3,12).

The interindividual variation in the risk and age at onset of HCC among chronic HBV carriers can be partly attributed to variability in exposures to aflatoxin-contaminated foods, alcohol, and cigarettes (6–9). The understanding of the genetic basis of HCC remains primitive. In our previous case-control studies—nested within a cohort study involving all of the HBV carriers included in the cohort study presented here as well as 2501 noncarriers of HBV—several polymorphic genes were found to influence the risk of HCC associated with specific environmental exposures, such as cigarette smoke, aflatoxin B₁, and alcohol (7,8,13–16). We recently observed a synergistic effect on HCC development for first-degree family

history of HCC with a p53 genetic polymorphism among chronic HBV carriers (16).

Other HCC-susceptibility genes may exist, with higher penetrance but lower frequency in the population, that might account for a small fraction of the HCC burden in the population. Two segregation analyses of HCC (17,18) have suggested the existence of a single major gene that could explain the mode of inheritance in some families after taking account of HBV infection. However, data on the magnitude and pattern of the familial aggregation of HCC have been limited. In this study, we used long-term follow-up data to evaluate the absolute HCC risks at a specified age for male HBV carriers with and without a family history of the disease in first-degree relatives. We also did a family study to assess risk for HCC and other types of cancer in relatives of chronic HBV carriers with HCC and of HBV carrier control subjects without HCC. The potential impact of family history of liver cirrhosis on the familial clustering of HCC was also evaluated.

SUBJECTS AND METHODS

Cohort Study

The cohort consisted of 4841 male HBV surface antigen (HBsAg) carriers aged 30–65 years who attended the Liver Unit of Chang-Gung Memorial Hospital and the Government Employee Central Clinics in Taipei, a metropolitan area in northern Taiwan, for regular health examination between August 1988 and June 1992. They all gave their consent to participate in this study and signed an informed consent form. Approximately 76.6% of the study participants were residents of Taipei, 21.2% were

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from districts near Taipei, and 2.2% were from more distant areas. The general design of this prospective investigation on HCC has already been described elsewhere (7,8,13–16). At the initial recruitment examination, in-person interviews were conducted by trained research assistants by use of a structured questionnaire. The recorded data include sociodemographic characteristics, lifetime habits of alcohol and tobacco use, as well as personal and family histories of major chronic diseases in Taiwan. Blood specimens, including white blood cells, serum, and plasma, were also obtained and frozen at -70°C until subsequent analysis. Participants were monitored for incident HCC by follow-up examinations (including an α -fetoprotein measurement and ultrasonography examination) every 6–12 months and confirmation from medical records and by searches of computer files of national death certification and cancer registry systems. Data on changes in habits of cigarette smoking and alcohol drinking, personal and family histories of major chronic diseases, and vital status of first-degree relatives were obtained during an in-person interview given before each follow-up examination. Although it was not specifically queried, no study participants mentioned that their first-degree relatives were also included in the cohort study at recruitment or follow-up interview of family medical histories. This study was approved by the Department of Health, Executive Yuan.

At the end of all the follow-up examinations, approximately 70% of the surviving HBsAg carriers continued to return for examination. By July 31, 1999, each cohort member had been followed-up for an average of 8.9 years. A total of 132 incident cases of HCC were identified. Ninety case subjects (68.2%) were identified by means of periodic follow-up examinations and 42 (31.8%) through secondary sources of information, including death records and reports from the national cancer registry system. HCC was diagnosed on the basis of either histologic finding or an elevated serum α -fetoprotein level (≥ 400 ng/mL) combined with at least one positive image on angiography, sonography, and/or computed tomography. Excluded from the analysis were 33 cohort members (eight of whom were detected with HCC during follow-up) with no available information on family history of HCC, which left a total of 4808 study subjects in the cohort analysis.

Case–Control Family Study

Basically, this family study used the demographic and morbidity/mortality data on their first-degree relatives obtained from the 124 HCC case subjects and 4684 HBsAg carriers unaffected by HCC as proband case and control subjects in the cohort study. Only 24 relatives of the HCC case subjects were reported to have HCC. This number was inadequate to allow precise estimation of the absolute risk of HCC at a specified age among relatives of case families. To increase statistical efficiency, we also consecutively recruited patients with newly diagnosed HCC treated at the Chang–Gung Memorial Hospital (Taipei, Taiwan), the National Taiwan University Hospital (Taipei), and the Taipei Veterans General Hospital (Taiwan). The three hospitals provided a major portion of medical care in Taipei City and its neighborhoods. Case subjects were eligible if the following criteria were met: 1) They were men aged less than 75 years; 2) they were HBsAg carriers;

and 3) they were not too ill and willing to cooperate by being personally interviewed. After the patients were informed about the study and had agreed to sign an informed consent form for participation, an in-person interview was scheduled within 2 weeks after diagnosis and a 10 to 20-mL sample of blood was collected from each patient under standardized protocols. Questionnaire data, including items of sociodemographic characteristics, lifestyle habits, and personal and family medical histories of major chronic diseases, were collected by trained research assistants. On average, less than 5% of the hospital patients meeting the inclusion criteria approached for interview refused to participate. Finally, a total of 429 HCC patients were recruited from the three participating hospitals. Among these patients, 154 (35.9%) were residents of Taipei City, 144 (33.6%) were from districts near Taipei, and the remaining 131 (30.5%) were from more distant areas. A family history of HCC in parents and/or siblings was reported by 75 (17.5%) patients. In total, there were 553 HCC case probands (124 from the cohort study plus 429 from hospitals) contributing family data in the case–control family study.

Family Data

Information on the family history in first-degree relatives (parents, siblings, and children) included the following: whether family members were still living; the age and sex of siblings and children, and, if deceased, their age at death; and whether a diagnosis of liver cirrhosis or cancer had been made in family members, the type of cancer, and the age at which the diagnosis was made. Because the occurrence of HCC may precede the diagnosis of underlying cirrhosis, liver cirrhosis that was reported to occur within 2 years before the diagnosis of HCC was not considered as positive for the history of liver cirrhosis. Half-brothers and half-sisters were not included in the analysis. Relatives who were currently less than 20 years old or who had died before age 20 years were also excluded from this study. Disease history of children was not considered in the present analysis, since only four sons and one daughter were reported to have had HCC.

Statistical Analysis

Analysis of risk among HBsAg carriers. We used the cohort study to estimate the cumulative risks of HCC for male HBsAg carriers who had a family history of HCC in first-degree relatives and for those without such a family history. The data on family history were based on the responses to the baseline questionnaire and were updated according to information on follow-up questionnaires. The cumulative HCC risk estimated from the disease-specific survival curve was assessed with the use of the product-limit method. The standard error of this risk estimate was calculated by a formula originally derived by Greenwood (19). For this analysis, each man was considered to be at risk for HCC from birth until his age at the date of termination of follow-up (if alive and unaffected), until his age at death (if dead and unaffected), or until his age at diagnosis of HCC. Comparison of cumulative risk curves between groups was evaluated by the log-rank test. Cox proportional hazards regression analysis was performed to estimate the rate ratio (RR), with a 95% confidence interval (CI) for family history of HCC. A test for trend in the RRs for HCC with

increasing number of affected relatives was based on the likelihood ratio test, with the number of relatives affected with HCC treated as a continuous variable in the Cox model. Estimates were made by use of both univariate and multivariate models. Because adjustments for age at recruitment, the total number of siblings in the family, educational levels, and habits of cigarette smoking and alcohol drinking had little effect on the relative risk estimates of HCC for a family history of HCC, we sometimes just present the results from the multivariate analysis. Statistical significance was set at the 5% level; all *P* values presented are two-sided.

Analysis of risk among relatives of case and control subjects. Data from the case–control family study were used to evaluate differences in the occurrence of liver cirrhosis, HCC, and other types of cancer among relatives between case and control families. The statistical significance of the difference in the mean age between two groups was determined by the Student's *t* test. The analysis of disease risk to relatives used two methods. Odds ratios (ORs) comparing disease risk in brothers, sisters, or all first-degree relatives combined of case subjects with the risk in the same relatives of control subjects were estimated by use of a logit marginal model taking account of within-family dependence as described by Liang and Zeger (20). We fitted the models by use of the GENMOD procedure of the statistical package PC-SAS version 6.12. In the marginal analysis, since the robust estimator of the covariance matrix of the regression coefficient estimates was used, the assumption about the covariance structure (or working correlation matrix) should have very little impact on the inference of the regression parameters. Initially, we analyzed the data by use of both the exchangeable and unstructured working correlation matrix. As expected, the two analyses were almost identical in estimating the regression coefficients and their standard errors. For brevity's sake, we presented in this report only the results from using the exchangeable correlation structure and reported an estimate of the within-cluster correlation coefficient to be .0154. The standard errors of the cumulative risks for relatives calculated were based on the assumption of independence of family members. This might result in inefficient estimation of the standard errors due to the within-family correlation. Despite not taking account of within-family dependence, however, the low estimate for the within-family correlation coefficients suggests that the estimates of standard error should not be distorted to a substantial degree. When risks to fathers and mothers were analyzed separately, an unconditional logistic regression model was used instead.

RESULTS

Risks in HBV Carriers With and Without Family History of HCC

In the cohort analysis, 15 (78.9%) of the 19 case subjects with a first-degree family history of HCC had only one affected relative, and four case subjects (21.1%) had two or more affected relatives. Overall, the RR for family history of HCC was 2.58 (95% CI = 1.58–4.22).

The RR did not alter materially after adjustment was made for age at recruitment (continuous variable), the total number of siblings in the family, educational levels (senior high school and above, junior high school, or primary school and below), cigarette smoking, and alcohol drinking (RR = 2.41; 95% CI = 1.47–3.95). Risk increased as the number of affected relatives increased ($\chi^2 = 12.88$; P for trend = .0003). Compared with male HBV carriers without a first-degree family history of HCC, the multivariate RR was 2.09 (95% CI = 1.21–3.62) for those who had one relative with HCC; for those with two or more affected relatives, the multivariate RR was 5.55 (95% CI = 2.02–15.26).

Cumulative risk of HCC was greater for the HBsAg carriers with a family history of HCC than for those without ($P = .0001$). By 70 years of age, the cumulative risk for male HBV carriers with a first-degree relative affected with HCC was 235.6 per 1000 (95% CI = 95.3–375.9 per 1000), whereas the risk for those without HCC was 88.9 per 1000 (95% CI = 67.9–109.9 per 1000). No clear evidence existed that familial case subjects had an earlier age of onset of HCC than nonfamilial case subjects because of the lack of statistical power (Table 1).

Risk to Relatives of Case Subjects Compared With Relatives of Control Subjects

The mean (standard deviation [SD]) age at diagnosis of HCC for the case subjects identified by the cohort study and those case subjects selected from hospitals was 53.8 (9.1) and 51.2 (10.0), respectively ($P = .01$). The two groups of case subjects were also similar in the total number of relatives (mean [SD]: 6.1 [2.1] for cohort case subjects; 6.1 [2.2] for hospital case subjects) and the proportion having a family history of HCC in first-degree relatives (15.3% of cohort case subjects versus 17.5% of hospital case subjects; $P = .89$). We thus combined the two groups of case subjects to gain statistical efficiency.

Case and control subjects had similar numbers of relatives in each category of kinship and similar mean ages of fathers and mothers. The mean ages of brothers ($P = .0001$) and sisters ($P = .0001$) were significantly older in case families than in control families, as was expected because the case and control subjects were not individually matched or frequency matched on age; HCC case subjects generally are

Table 1. Cumulative risk (one per 1000) of HCC in a cohort of 4808 HBsAg-positive men aged 30–65 years (from 1988 through 1999)*

Family history	Age, y				
	30–39	40–49	50–59	60–69	≥70†
Negative					
No. at risk	4422	4415	2311	917	273
Person-years	44 201.5	34 658.5	15 131.0	5761.0	629.5
Cumulative No. of HCCs	6	33	63	101	105
Cumulative risk	1.4	9.4	28.3	88.9	111.0
95% CI of cumulative risk	0.3–2.4	6.1–12.6	20.7–35.9	67.9–109.9	78.9–143.1
Positive					
No. at risk	386	386	203	58	8
Person-years	3860.0	3150.5	1196.5	283.0	12.0
Cumulative No. of HCCs	0	8	13	19	19
Cumulative risk	0.0	27.1	67.1	235.6	235.6
95% CI of cumulative risk	—	8.3–45.9	27.7–106.5	95.3–375.9	95.3–375.9
Positive versus negative					
Risk ratio	0	2.88	2.37	2.65	2.12
95% CI	—	1.34–6.29	1.24–4.52	1.40–5.03	1.09–4.12

*HCC = hepatocellular carcinoma, HBsAg = hepatitis B surface antigen, and CI = confidence interval.

†In the group without a first-degree family history of HCC, no HCC cases occurred after 73 years of age. In the group positive for the family history, no HCC cases occurred after 68 years of age.

older than unaffected persons (Table 2). The ORs for HCC and liver cirrhosis for relatives of case probands compared with relatives of control probands are shown in Table 3. There was a greater risk of HCC and liver cirrhosis among relatives of case subjects than among relatives of control subjects. When different types of relatives were analyzed separately, both HCC and liver cirrhosis risks statistically significantly increased for mothers and siblings of case subjects but not for fathers.

Cumulative HCC risk to relatives was greater for case subjects than for control subjects ($P = .0001$) and was greater for case subjects diagnosed at less than 50 years of age than for those diagnosed at greater than or equal to 50 years of age ($P = .047$). The risk ratio comparing the age-specific risk of HCC in relatives of case subjects with the risk in relatives of control subjects was as high as 6.0 by the age of 30 years, and it gradually decreased with advancing age to 1.98 by the age of 80 years. Similarly, the difference in the risk among relatives between case

subjects diagnosed at less than 50 years of age and those diagnosed at greater than or equal to 50 years of age was the greatest at young ages (Table 4).

No statistically significant difference existed in the overall occurrence of non-HCC malignancy between the relatives of case subjects and the relatives of control subjects. Case families had no statistically significant excess of risk for any individual types of non-HCC malignancy (data not shown).

DISCUSSION

The major finding of this study was the profound familial effect for the development of HCC. Evaluation of family history of cancer and cancer risk has been primarily based on recalled cancer history among first-degree relatives. Although a nested case-control study conducted in China has reported a greater risk of HCC for individuals with either affected first-degree or second-degree relatives (21), accurate ascertainment of cancer history

Table 2. The Taiwan HCC case-control family study: number and mean age of evaluable first-degree relatives of HBsAg-positive case and control subjects at death or at the time of survey*

Kinship category	Case families (n = 553)		Control families (n = 4684)	
	No. (%)	Mean age, y (SD)	No. (%)	Mean age, y (SD)
All relatives	3368 (100.0)		29 954 (100.0)	
Fathers	518 (15.4)	68.1 (13.9)	4501 (15.0)	67.5 (12.2)
Mothers	522 (15.5)	69.1 (13.5)	4527 (15.1)	68.3 (11.4)
Brothers	1213 (36.0)	50.0 (11.9)	10 830 (36.2)	45.9 (11.7)
Sisters	1115 (33.1)	50.5 (11.5)	10 096 (33.7)	45.8 (11.6)

*HCC = hepatocellular carcinoma, HBsAg = hepatitis B surface antigen, and SD = standard deviation.

Table 3. Adjusted ORs for HCC and liver cirrhosis according to kinship for relatives of HBsAg-positive case subjects compared with relatives of HBsAg-positive control subjects in the Taiwan HCC case-control family study*

Relatives	Case families (n = 553)		Control families (n = 4684)		OR†	95% CI
	No.	%	No.	%		
Mother						
HCC	21	4.0	71	1.6	2.64	1.60–4.34
Liver cirrhosis	17	3.3	52	1.2	2.92	1.67–5.08
Father						
HCC	25	4.8	159	3.5	1.36	0.86–2.11
Liver cirrhosis	14	2.7	125	2.8	0.96	0.54–1.68
Brother						
HCC	54	4.5	133	1.2	3.73	2.64–5.27
Liver cirrhosis	29	2.4	51	0.5	4.69	2.83–7.79
Sister						
HCC	12	1.1	22	0.2	4.55	2.22–9.31
Liver cirrhosis	4	0.4	4	0.04	6.80	1.52–30.40
All relatives						
HCC	112	3.3	385	1.3	2.57	2.03–3.25
Liver cirrhosis	64	1.9	232	0.8	2.29	1.68–3.11

*HCC = hepatocellular carcinoma, HBsAg = hepatitis B surface antigen, OR = odds ratio, and CI = confidence interval. The referent category for each OR is the number of first-degree relatives of case or control subjects (see Table 2) minus the number affected with the specific disease.

†When different types of relatives were analyzed separately, ORs were adjusted for age. For all relatives, ORs were adjusted for the age and sex of the relative.

about relatives with kinship order greater than first-degree is feasible only when genealogy data are available that can be linked to a cancer registry computerized

system. For minimization of the possibility of the recall bias, only first-degree relatives were included in the analysis. We used both the cohort study and the

case-control study designs to investigate familial risk. It is possible that those who received the diagnosis recently were more likely to be aware of a family history of cancer than were control subjects, resulting in an inflated estimate of the excess risk of HCC among relatives of case subjects. However, control subjects in the case-control family study were HBV carriers who participated in a long-term follow-up study for early diagnosis of HCC. It is plausible that these control subjects may be relatively familiar with the clinical manifestation and diagnosis of HCC. Thus, the likelihood was rather low that the estimate of the excess risk of HCC among relatives of case subjects was inflated as a result of a better awareness of a family history of cancer for case subjects compared with control subjects.

The prospective nature of the cohort study eliminated the recall bias because of differential reporting of family history of cancer by case and control subjects in a retrospective design. In the cohort study, however, the method of using family-history information did not take into account the possible effects of family structure and the age differences among families in assessing familial risk of HCC. In the case-control family study, we

Table 4. Cumulative risk (one per 1000) of HCC among first-degree relatives of HBsAg-positive case and control subjects in the Taiwan HCC case-control family study*

Subjects	Age of first-degree relatives, y					
	20–29	30–39	40–49	50–59	60–69	70–80
Control subjects						
No. of relatives at risk	29 954	28 660	22 966	15 702	10 179	4 921
Cumulative No. of HCCs	7	42	128	237	339	385
Cumulative risk	0.2	1.6	6.1	14.6	27.8	42.0
95% CI of cumulative risk	0.06–0.4	1.1–2.1	5.0–7.2	12.7–16.5	24.6–31.0	36.6–47.4
Case subjects						
No. of relatives at risk	3 368	3 287	2 907	2 132	1 387	681
Cumulative No. of HCCs	4	15	39	72	99	112
Cumulative risk	1.2	4.7	14.4	33.4	57.7	83.0
95% CI of cumulative risk	0.03–2.4	2.3–7.1	9.9–18.9	25.6–41.2	45.7–69.7	64.2–101.8
Case subjects diagnosed at <50 y of age						
No. of relatives at risk	1 344	1 282	1 011	630	389	190
Cumulative No. of HCCs	4	10	14	29	38	43
Cumulative risk	3.1	8.1	12.8	42.4	70.9	100.2
95% CI of cumulative risk	0.06–6.1	3.1–13.1	6.0–19.6	26.2–58.6	46.4–95.4	65.3–135.1
Case subjects diagnosed at ≥50 y of age						
No. of relatives at risk	2 024	2 005	1 896	1 502	998	491
Cumulative No. of HCCs	0	5	25	43	61	69
Cumulative risk	0	2.6	14.4	29.2	51.8	74.3
95% CI of cumulative risk	—	0.3–4.8	8.8–20.0	20.4–38.0	38.2–65.4	53.1–95.9
Case versus control subjects						
Risk ratio	6.00	2.94	2.36	2.29	2.08	1.98
95% CI	1.49–17.22	1.63–5.29	1.65–3.39	1.75–2.99	1.64–2.63	1.52–2.56
Case subjects diagnosed at <50 versus ≥50 y of age						
Risk ratio	∞	3.12	0.89	1.45	1.37	1.35
95% CI	—	1.08–9.26	0.46–1.72	0.89–2.36	0.89–2.11	0.86–2.11

*HCC = hepatocellular carcinoma, CI = confidence interval, and HBsAg = hepatitis B surface antigen.

treated each relative ascertained through case and control subjects as the analytic unit. The increased risk of HCC in relatives of case subjects was present, even after allowing age and sex in the model.

Although it has been suggested that chronic infection with HBV may be through transmission of this virus between siblings during early childhood in certain areas (22), mother-to-child vertical transmission has been well established as the major route of acquiring chronic HBV infection in Taiwan (23–25). It is estimated that 30%–85% of the babies born to HBsAg-positive mothers become HBsAg carriers, depending on the status of the maternal HBV e antigen (24). Given the importance of the HBsAg carrier status for HCC risk (2,4), chronic HBV infection is an important source of familial effects for HCC. This study attempted to remove the greatest environmental risk factor for HCC by restricting the analysis to chronic HBV carriers and their first-degree relatives. Although we did not have data on the HBsAg carrier status of family members because of the difficulty of collecting blood samples for all family members, the mothers and siblings of the HBV carrier case and control subjects were very likely to be HBsAg carriers (25).

Dietary habits and other behaviors associated with HCC that cluster in families may also account for some of the observed familial aggregation of the disease. Exposure to aflatoxin-contaminated foods, cigarette smoking, and alcohol drinking are such variables that have been implicated in the etiology of HCC (6–9). The increased HCC risk was present not only in male relatives of case subjects but also in female relatives whose prevalence of smoking or drinking is believed to be rather low. Furthermore, the familial effect for the development of HCC among male HBV carriers did not show substantial changes when we adjusted for smoking and drinking in the analysis. Therefore, the association between family history of HCC and HCC development is unlikely to be explained on the basis of confounding by these two factors. In nested case–control studies (6–8), the ORs of HCC associated with different levels of aflatoxin exposure measured by use of urinary/serum biomarkers ranged from 3 to 6. No effort in this study was made to investigate aflatoxins because it was not feasible to assess aflatoxin exposure by using biomarkers for thousands of

relatives. However, simulation studies (26,27) have shown that a single environmental risk 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.

It is possible that, in the absence of environmental factors, a familial tendency for HCC is not expressed. However, the findings of a greater risk in relatives of case subjects diagnosed before age 50 years and the more remarkable difference in the risk of relatives between case and control families at young ages suggest that transmissible genetic factors may be involved in the development of HCC in some families of HBV carriers with a family history of HCC. Segregation analyses of HCC in Chinese and Alaskan families have suggested a single gene model that could explain the mode of inheritance in some families after taking account of the HBV infection, although no single mode of inheritance has been consistently identified. They also demonstrated an HBV–major gene interaction (17,18). Regardless of genotype, the risk for persons not infected with HBV was virtually zero (17). HCC usually develops after several decades of chronic HBV infection accompanied by the signs of hepatocyte necrosis, inflammation, and regenerative hyperplasia (3,4). It is possible that the chronic necroinflammatory process caused by persistent HBV infection creates a mutagenic internal environment that unmasks a genetic predisposition to HCC. The higher HCC risks for mothers and siblings than for fathers observed in this study, therefore, may be simply explained by a much higher HBsAg carrier rate among the mothers and siblings of HBV carriers than among the fathers as a result of vertical transmission of the virus (23–25).

The molecular basis for such genetic predisposition toward HCC remains to be elucidated. We can hypothesize that the HCC-susceptibility gene may be specific for hepatocarcinogenesis, since no statistically significant excess of other types of cancer was observed in the case families. However, the average age at onset of HCC in Taiwan is about 50 years, while most other common cancers, such as those of the lung, stomach, and large bowel, primarily occur at ages 60 years or older. Because of the early-onset characteristic of HCC and its high fatality, we

should not observe a marked familial clustering for cancers of other anatomic sites in the case families. Our study also demonstrated about a twofold higher risk of liver cirrhosis in case families than in control families. Liver cirrhosis is the most important premalignant lesion of HCC (5). Two rare genetic syndromes—hemochromatosis and α 1-antitrypsin deficiency—characterized by a high risk of developing liver cirrhosis, have been associated with an increased risk of HCC in Western populations (28,29). However, Chinese HCC patients are rarely reported to have such genetic syndromes. We have identified several polymorphic genes involved in susceptibility to the effect of exposure to certain environmental risk factors (7,8,13–16). This gene–environment interaction might be expressed as a higher familial risk for the first-degree relatives. On the other hand, many allele loss studies on HCC have been carried out (30,31). However, an association between loss of heterozygosity on particular chromosome arms and familial history of HCC in patients with this disease remains to be determined (32).

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NOTES

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