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Family history of liver cancer may modify the association between HBV infection and liver cancer in a Chinese population

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Abstract

Background & Aims: The potential interaction between family history of liver cancer and HBV infection on liver cancer has not been fully examined.

Methods: We conducted a population-based case-control study composed of 2011 liver cancer cases and 7933 controls in Jiangsu province, China from 2003 to 2010. Data on major risk or protective factors were collected and HBV/HCV sero-markers were assayed using blood samples. Semi-Bayes (SB) adjustments were applied to provide posterior estimates.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

Results: Both family history of liver cancer (adjusted odds ratios [OR]: 4.32, 95% confidence intervals [CI]: 3.25–5.73) and hepatitis B surface antigen (HBsAg) positivity (adjusted OR: 9.94, 95% CI: 8.33–11.87) were strongly associated with liver cancer development. For individuals with different combinations of serological markers, the adjusted ORs were 8.45 (95% CI: 5.16–13.82) for HBsAg- and HBcAb-positive; 7.57 (95% CI: 4.87–11.77) for HBsAg-, HBeAg- and HBcAb-positive; and 3.62 (95% CI: 2.47–5.31) for HBsAg-, HBeAb- and HBcAb-positive, compared to all negatives in HBV serological markers. One log increase in HBV DNA level was associated with 17% increased risk (adjusted OR: 1.17, 95% CI: 1.03–1.32). The SB-adjusted OR of HBV-positive individuals with family history of liver cancer was 41.34 (95% posterior interval [PI]: 23.69–72.12) compared with those HBV-negative without family history. Relative excess risk due to additive interaction, the attributable proportion and synergy index were 73.13, 0.87 and 8.04 respectively. Adjusted ratio of OR for multipli-cative interaction was 2.84 (95% CI: 1.41–5.75).

Conclusions: Super-additive and super-multiplicative interactions may exist between family history of liver cancer and HBV infection on the development of liver cancer.

Keywords

family history; hepatitis B Virus; hepatocellular carcinoma; interaction; serological marker

1 | INTRODUCTION

Primary liver cancer was the sixth most common neoplasm and the fourth leading cause of cancer death with about 841 000 new cases and 781 000 deaths worldwide in 2018.[1] More than all other countries in the world combined, China accounts for almost half of all newly diagnosed cases (46.7%) and liver cancer deaths (47.2%) each year.[1] The heavy burden concurs with high prevalence of established risk factors for liver cancer, including chronic hepatitis, alcohol consumption as well as family history of liver cancer.

Hepatitis virus infections are leading etiological factors for liver cancer,[2,3] and it has been estimated by our group that HBV is responsible for 44% and 54% of liver cancer cases worldwide and in China, respectively, and HCV is responsible for 21% and 18%.[4] In Chinese population, the prevalence of hepatitis B surface antigen (HBsAg) positivity among younger than 60 year olds was 7.2% esti-mated in 2006,[5] and the prevalence of HCV antibody positivity was 0.43%.[6] As the most important marker indicating HBV infection, the association between HBsAg and liver cancer has been fully studied, and IARC reported relative risks ranging from 9.6 to 74 in cohort studies.[7] Other serological markers for HBV infection including HBsAb, HBeAg, HBeAb, HBcAb and HBV DNA load were universally used in clinical settings to assess the progression of hepatitis B. However, liver cancer risk for people with different combinations of these sero-markers has not been fully studied,[7] motivating a more comprehensive evaluation.

Accumulated evidence showed that liver cancer and its risk factors tended to have family aggregation. Having family history of liver cancer was consistently associated with liver cancer risk by two- to threefolds,[8–10] suggesting that either genetic inheritance or shared environmental exposures or both are associated with the disease. Shared environmental exposures may include behavioural factors such as alcohol and tobacco use, for which the

association has been explored in literature and by our study,[11–13] and may also include carcinogens such as aflatoxin B_1 (AFB_1) intake from food or microcystin intake from water.[8,14,15] Like other cancers, liver carcinogenesis is a long-term multistep process and risk factors might act jointly, influencing risk for liver cancer. For example, our earlier study reported interactions between HBV infection and tobacco smoking as well as alcohol drinking.[13,16,17] Synergistic effects between family history of liver cancer and HBV infection had been reported in limited studies.[18] However, joint association and potential interaction between family history of liver cancer and a variety of combinations of HBV sero-markers and HBV DNA have never been investigated. Precise risk stratification for liver cancer and more targeted prevention and treatment of hepatitis are difficult to achieve, especially in countries with heavy burden from hepatitis and liver cancer such as China. We conducted a population-based case-control study in four counties of Jiangsu Province, China with 2011 liver cancer cases and 7933 controls to evaluate the potential interactions between family history of liver cancer and HBV infection sero-markers on liver cancer development. We performed semi-Bayes adjustment to reduce possibility of false positive findings.[19]

2 | METHODS

2.1 | Study design and participants

A population-based case-control study was conducted in four counties: Dafeng, Ganyu, Chuzhou and Tongshan in Jiangsu Province, China from 2003 to 2010. These four counties are located in northern Jiangsu with the following population sizes: 0.71 million in Dafeng, 0.95 million in Ganyu, 0.98 million in Chuzhou and 1.14 million in Tongshan (6th national census data, 2010). Jiangsu is an eastern coastal province in China with a cancer mortality of 194 per 100 000 in 2010.[20] Since 1970s, cancer has been the leading cause of death in this province, with liver cancer mortality ranked third among all cancers in 2010. Due to the heavy burden of cancer in this region, county-level cancer registries were established in the late 1990s. This study was originally designed to explore aetiological heterogeneities in the risks of four common cancers, including cancers of oesophagus, stomach, lung and liver, in these four counties. The overall design of the study is described in detail previously.[21] In summary, eligible cases were identified and recruited based on the information from the four county cancer registries between January 2003 and December 2010. The inclusion criteria were: (a) aged 18 years or older; (b) local residents for at least 5 years; and (c) newly diagnosed as primary liver cancer within past 12 months. Eligible controls were randomly selected from a roster of local residents from county-specific demographical databases. The controls were originally individually matched to cases by gender and age (±5 years) for each cancer site. In this study, we performed analysis by combining the controls from the four parallel case-control studies. Individuals previously diagnosed with any cancer were excluded. A total of 2011 cases with liver cancer and 7933 healthy controls were included in the study. The overall participation rates were 37% for liver cancer cases reported during 2003 and 2010, and 87% for controls.

2.2 | Data collection

The study was approved by the Institutional Review Board of Jiangsu Provincial Health Department and Human Subject Protection Committee of University of California, Los

Angeles. Written informed consent was obtained from each participant. A standard questionnaire for face-to-face interviews was used to collect epidemiological data by trained personnel. The epidemiological data collected by the questionnaire include: (a) socio-demographic characteristics; (b) potential liver cancer risk factors including alcohol drinking, smoking, family history of liver cancer, history of mildew-contaminated food intake, history of raw water drinking, etc; and (c) dietary history and lifestyle. For family history of liver cancer, the participants were asked if any relatives in their family, including parents, children, grandparents, siblings and cousins on both parents' side had ever had liver cancer diagnosis. And family history of liver cancer in first-degree relatives was limited to liver cancer diagnosis to parents, children and siblings. Quality control of data collection was performed quarterly and 10% of the participants were randomly selected for re-interview, and results indicated an overall accuracy of 96% for cases and 97% for controls.[21]

2.3 | Serological measurements

After the interview, 6–8 mL of blood was drawn and centrifuged. The serum samples were then kept at −20°C. Of a total of 9944, 7745 (78% of 9944) participants, including 1216 (60% of 2011) cases and 6529 (82% of 7933) controls had blood samples collected. The collection rates of blood samples differed by gender (male: 77%; female: 80%), county of residence (79% of participants from Dafeng, 68% from Ganyu, 67% from Chuzhou, and 90% from Tongshan), age, and per capita family income 10 years prior to the study, but not by level of education, marital status, or body mass index (BMI). Serum HBsAg, HBsAb, HBeAg, HBeAb, HBcAb and HCV antibodies (HCV-Ab) were assayed using enzyme-linked immunosorbent assay (ELISA) (Shanghai Kehua Diagnostic Medical Products Co., Ltd., China) according to the manufacturer's protocol at Jiangsu CDC. Triple or double negative controls and one positive control were used in each 96-well testing plate. About 7689 participants, including 1211 liver cancer cases and 6478 controls had enough serum samples for the measurements of the six ELISA-measured markers. For those HBsAg-positive, serum HBV DNA was extracted and quantified by real-time polymerase chain reaction (PCR) technique (Quantitative Diagnostic Kit for Hepatitis B Virus DNA, PCR-Fluorescent Probing, Qiagen, Shenzhen, China). The limit of detection was 500 IU/mL and the linear range of HBV DNA quantification was between 1.0×10^3 and 5.0×10^7 IU/mL. HBV DNA level greater than 10000 IU/mL was defined as high viral load.[22]

2.4 | Statistical analyses

Categorical variables were compared using Chi-squared tests. Unconditional logistic regression was used to estimate the crude odds ratios (OR) and adjusted ORs with their 95% confidence intervals (CI).

The potential confounding variables were adjusted for in the models including age (continuous), gender (male = 0, female = 1), level of education (illiteracy = 0, primary school = 1, middle school = 2, high school and college = 3, entered as dummy variables), marital status (in marriage = 1, single, divorced or wid-owed = 0), per capita family income 10 years prior to the study (RMB Yuan/year, continuous), BMI (continuous), family history of liver cancer (yes = 1, no = 0), pack-year of smoking (continuous), weekly ethanol consumption in 1990s (mL/week, continuous), history of mildew-contaminated food intake

(yes = 1, no = 0), history of raw water drinking (yes = 1, no = 0), HBsAg status (positive = 1, negative = 0), anti-HCV status (positive = 1, negative = 0) and county of residence (Dafeng = 1, Ganyu = 2, Chuzhou = 3, Tongshan = 4, entered the model as dummy variables). The observations with missing values were not included in the multiple regression model for each analysis.

For examining the potential interactions, relative excess risk due to interaction (RERI), attributable proportion because of in-teraction (AP), and synergy index (S) with 95% CI were calculated for interaction on the additive scale.[23] Let OR_{ij} be an approxi-mation for the risk ratio (RR) in exposure category i,j, OR_{11}, OR_{10}, OR_{01}, OR_{00} be the OR for each exposure categories, and $OR_{00} = 1$. $RERI = OR_{11} - OR_{10} - OR_{01} + 1$, $AP = RERI/OR_{11}$, and $S = [OR_{11} - 1]/ [(OR_{10} - 1) + (OR_{01} - 1)]$.[23] The ratio of the odds ratios (ROR) was calculated by logistic regression models to examine interaction on the multiplicative scale.

In order to decrease the possibility of false positive findings, we employed the semi-Bayes adjustment method to generate posterior estimates of the effect measures using information-weighted averaging.[19] The priors used were from a meta-analysis published in 2005 based on a search of both the Chinese and English liter-ature on risk factors of liver cancer in Chinese populations from 1966 to 2003.[8] For family history of liver cancer, the prior OR was 3.49 (95% CI: 2.68–4.53). For HBsAg positivity the prior OR was 11.34 (95% CI: 8.72–14.75), and for HCV-Ab positivity the prior OR was 4.28 (95% CI: 3.30–5.56). For history of mildew-contaminated food intake, the OR for aflatoxin exposure was used as the prior (OR = 1.80, 95% CI: 1.44 – 2.25). For history of raw water drinking, the OR for drink water from pond was used as the prior (OR = 1.77, 95% CI: 1.09–2.87). Another three sets of null priors [Prior OR (95% limits)]: 1 (1/2, 2), 1 (1/4, 4) and 1 (1/16, 16) were also used. These allow examining how results vary as variances of the priors change.[19]

The adjusted ORs were estimated as an approximation for the corresponding RR, and the prevalence (P) of risk factor in the control group was used as the population prevalence. The attributable risk fraction (AR%) was calculated as (OR-1)/OR, and the population attributable risk (PAR) was calculated as P*(OR-1)/ [P*(OR-1)+1].

Statistical analyses were performed using the SAS 9.3 statistical software (SAS Institute, Inc, Cary, NC). A two-tailed *P*-value of less than 0.05 was considered as statistically significant.

3 | RESULTS

3.1 | Socio-demographic characteristics

A total of 2011 cases and 7933 controls were included in this study, with 73% male and a mean age of 63 years. Among them, 1211 cases and 6478 controls had sufficient serum samples for measurement of six HBV/HCV infection sero-markers. Table 1 showed the distribution of demographic and socio-economic characteristics of the cases and the controls. In the original cancer-specific studies, the cases and the controls were individually matched by age and gender. After combining the four groups of controls, the cases tended to be younger and have a larger proportion of males than the controls. The two groups also

differed in county of residence, marital status, level of education, per capita family income 10 years prior to the study and BMI. And more cases tended to drink and smoke than the controls.

3.2 | Family history of liver cancer

Family history of liver cancer showed an adjusted OR of 4.32 (95% CI: 3.25–5.73) and a posterior OR of 3.85 (95% PI: 3.18–4.67), after controlled for major confounding factors and semi-Bayes adjustment using informative prior (Table 2). Having one family member (OR: 4.24, 95% CI: 3.14–5.74) and two (OR: 4.06, 95% CI: 1.76–9.33) with liver cancer was associated with about four times the risk compared to none, while having three members with liver cancer history further increased the risk (OR: 7.94, 95% CI: 1.83–34.46) (P_{for} trend < 0.001). Family history of liver cancer in first-degree relatives showed adjusted OR of 5.12 (95% CI: 3.71–7.07), with semi-Bayes adjusted posterior OR (SB-OR) of 4.07 [95% posterior interval (PI): 3.32–4.98]. And having one (OR: 5.07, 95% CI: 3.59–7.15), two (OR: 5.51, 95% CI: 2.09–14.58) and three (OR: 5.41, 95% CI: 1.07–27.49) first-degree relatives with liver cancer history was associated with about five times the cancer risk ($P_{\text{for trend}}$ < 0.001).

3.3 | HBV/HCV infection

HBsAg positivity was confirmed to be a strong risk factor for liver cancer with an adjusted OR of 9.94 (95% CI: 8.33–11.87), and a SB- OR of 10.36 (95% PI: 8.94–12.00) using the informative prior. A total of 524 liver cancer cases and 425 controls were HBsAg-positive. The characteristics for HBsAg-positive cases and controls are shown in Table S1. Eleven liver cancer cases and 53 controls were HCV-Ab- positive, and the aOR between HCV infection and liver cancer was 1.36 (95% CI: 0.61–3.06), with a SB-OR of 3.84 (95% PI: 3.00–4.92). (Table 2).

The associations observed between family history of liver cancer, HBV infection and liver cancer were both found in men and women. (Table 2).

3.4 | Detailed examination on sero-markers for HBV infection

Higher proportion of cases was tested positive for HBsAg (36.2% vs 6.5% in controls), HBeAg (14.4% vs 1.7%) and HBeAb (28.7% vs 14.8%), while more controls were tested positive for H BsAb (55.6% vs 36.2% in cases) and HBcAb (93.0% vs 91.3%). There were nine common combinations and 14 relatively rare combinations of HBV markers, and the association between the nine common combinations and the risk of liver cancer was examined. Compared to those who tested negative for all five markers (HBsAg, HBsAb, HBeAg, HBeAb and HBcAb), those who were positive for HBsAg and HBcAb showed the highest risk for liver cancer (adjusted OR: 8.45, 95% CI: 5.16–13.82), followed by those positive for HBsAg, HBeAg and HBcAb (adjusted OR: 7.57, 95% CI: 4.87–11.77) and those positive for HBsAg, HBeAb and HBcAb (adjusted OR: 3.62, 95% CI: 2.47–5.31). Those who were positive for HBcAb only (adjusted OR: 0.42, 95% CI: 0.29–0.60), positive for HBsAb, HBeAb and HBcAb (adjusted OR: 0.63, 95% CI: 0.42–0.94), and positive for HBsAb and HBcAb (adjusted OR: 0.48, 95% CI: 0.34–0.67) showed decreased risk for liver cancer, after controlling for potential confounding variables. And these associations

remained significant after semi-Bayes adjustment with null prior: 1 (1/4, 4). (Table 3 and Figure 1A).

The association between serum HBV DNA level and liver cancer was examined (Table 4 and Figure 1B). After controlling for potential confounding variables, one log increase in serum HBV DNA level was associated with increased risk of liver (adjusted OR = 1.17, 95% CI: 1.03–1.32) among those with detectable HBV DNA. When examining across viral load levels, the liver cancer risk increased with the increase in viral load for the first four groups, and then decreased for the highest two groups. In detail, the adjusted ORs were 2.10 (95% CI: 0.92–4.76) for 500–10^3 IU/mL group, 2.18 (95% CI: 1.27–3.72) for 10^3-10^4 IU/mL group, 5.40 (95% CI: 2.98–9.79) for 10^4-10^5 IU/mL group, 10.37 (95% CI: 5.65–19.01) for 10^5-10^6 IU/mL group, 8.52 (95% CI: 4.66–15.57) for 10^6-10^7 IU/mL group, and 2.39 (95% CI: 1.27–4.50) for >10^7 IU/mL group, all compared to those with viral load under limit of detection ($P_{\text{for trend}} < 0.001$). (Table 4 and Figure 1B).

3.5 | Combined association of family history of liver cancer and HBV sero-markers with liver cancer

Combined effects of family history of liver cancer and different combinations of HBV serological markers including HBsAg, HBeAg, HBeAb, HBV DNA levels on liver cancer were examined. (Table 5 and Figure 2) The risk of liver cancer increased among those with family history of liver cancer across strata of HBV infection mark-ers, and was highest among those with family history of liver cancer, HBsAg-positive, HBeAg-positive, and HBV DNA > 10000 IU/ mL (aOR = 130.21, 95% CI: 30.37–558.24; SB-OR = 10.13, 95% PI: 3.71–27.65) and among those with family history of liver cancer, HBsAg-positive, HBeAg-positive and HBeAb-negative (aOR = 158.73, 95% CI: 37.04–680.28; SB-OR = 11.14, 95% PI: 4.08–30.40).

3.6 | Interaction between family history of liver cancer and HBV infection on the development of liver cancer

The potential interactions between family history of liver cancer with HBsAg-positive, HBeAg-positive or HBV DNA over 10000 IU/mL on liver cancer risk were examined on both additive scale and multi-plicative scale (Table 6). Compared to HBsAg-negative participants without family history of liver cancer, HBsAg-negative participants with family history showed aOR of 3.25 (95% CI: 2.29–4.62), HBsAg-positive participants without family history showed aOR of 9.14 (95% CI: 7.60–11.00), and those HBsAg-positive with family history of liver cancer showed highest aOR of 84.53 (95% CI: 46.03–155.22). The interaction between family history of liver cancer and HBsAg positivity was both super-additive, reporting RERI of 73.13 (95% CI: 21.96–124.30), AP of 0.87 (95% CI: 0.78–0.95) and S of 8.04 (95% CI: 4.29–15.04), and super-multiplicative, reporting ROR of 2.84 (95% CI: 1.41–5.75). Similar positive interactions on additive scale but not on multiplicative scale were observed between family history of liver cancer and HBeAg positivity, and between family history and HBV DNA > 10000 IU/mL.

3.7 | Other liver diseases

More liver cancer cases reported to have history of hepatitis (24.5% vs 3.6%, $P < 0.001$), fatty liver disease (1.5% vs 0.5%, $P < 0.001$) and liver cirrhosis (7.0% vs 0.1%, $P < 0.001$) than the controls. Among liver cancer cases, participants with family history of liver cancer reported higher proportion of history of hepatitis than those without family history of liver cancer (39.5% vs 22.1%, $P < 0.001$), and similar difference was found among the controls (7.6% vs 3.5%, $P < 0.001$). (Table S2).

3.8 | Other family-aggregated risk factors

History of raw water drinking showed adjusted OR of 1.33 (95% CI: 1.13–1.55) and posterior OR of 1.37 (95% PI: 1.18–1.59) with liver cancer using informative prior, while history of mildew-contaminated food intake showed adjusted OR of 1.17 (95% CI: 0.89–1.54) and posterior OR of 1.52 (95% PI: 1.28–1.80). (Table 2) A super-additive interaction between HBsAg-positive and history of raw water drinking was observed, reporting RERI of 4.45 (95% CI: 0.99–7.90), AP of 0.33 (95% CI: 0.12–0.53) and S of 1.55 (95% CI: 1.11–2.16). Sub-additive interaction and sub-multiplicative interaction between family history of liver cancer and raw water drinking were observed, reporting S of 0.49 (95% CI: 0.26–0.94) and ROR of 0.41 (95% CI: 0.23–0.73).

3.9 | Population attributable risk

The attributable risk fraction was 89.9% for HBsAg-positive and 80.5% for having family history of liver cancer. And the PAR was 36.8% for HBsAg-positive and 11.3% for having family history of liver cancer in Chinese population.

4 | DISCUSSION

This population-based case-control study is among the first studies to fully examine the associations between liver cancer risk and serological patterns of HBV/HCV infections and potential effect-measure modification between family history of liver cancer and HBV seromarkers on liver cancer risk by using a large sample size in a Chinese population. It was also the first to employ semi-Bayes adjustment to provide posterior estimates for these associations.

With comprehensive control of major potential confounders, being HBsAg-positive was confirmed to be a strong risk factor for liver cancer, and the risk increased with higher level of HBV DNA. These were largely in line with the results of the previous studies.[8,24–33] In particular, the Taiwan REVEAL-HBV study, the Jiangsu Qidong cohort study and a meta-analysis reported dose-dependent relationship between HBV DNA and increased liver cancer risk, then a decrease in magnitude of the association in the highest DNA level groups, [22,32,34–36] which is in concordance with our observations. On the other hand, as another major viral cause of liver cancer world-wide especially in western countries, (4) HCV infection showed a very low prevalence in this population, and there is no significant association detected between HCV and liver cancer in this analysis. . However, we still include the HCV infection status in all analyses for confounding control.

In our study, having family history of liver cancer showed four times the risk of liver cancer, and if it was from first-degree relative, the risk increase was five times, which was stronger than the associations reported in former observations.[8–10] Inheritance is believed to play a role in liver carcinogenesis and genetic epidemiologic studies kept searching for and reporting susceptible loci.[37,38] Meanwhile, family-aggregated environmental exposures also increased the risk, and the associations between aflatoxin intake though mildew-contaminated food, unsafe raw water and liver cancer risk were confirmed in this study and previous literature.[8–10,14]

The sufficient sample size made it possible to examine liver cancer risk by not only HBV infection sero-markers individually, but also by their various patterns and further combinations with family history of liver cancer. We reported liver cancer risk for people in different combinations of HBV sero-markers and family history, providing epidemiologic evidence for risk stratification in HBV infection. We also showed that family history modified the association between HBV infection and liver cancer. A super-additive and super-multiplicative interaction between HBsAg-positive status and family history of liver cancer was detected, and similarly, the interactions were found in examining the HBeAg status, HBV DNA levels. These observations with a more comprehensive confounding control were in concordance to the findings reported by the cohort study in Taiwan.[18] The synergistic effects of family history of liver cancer and HBV infection on liver cancer risk might suggest genetic susceptibility, as well as possibility of vertical transmission of the virus from mother to child and shared environmental exposures in the family.

We reported the PAR of 36.8% for HBsAg-positive and of 11.3% for having family history of liver cancer in Chinese population. The PAR for HBV infection is lower than the previously published overall estimate of 53.8% for China.[4] It is probable that the effect size and prevalence for HBsAg in the Jiangsu study are different from the national estimate. However, HBV infection is still the most important risk factor for liver cancer in Chinese population. And we firstly reported the PAR for family history of liver cancer, appealing for further studies on genetic and environmental-aggregated risk factors.

Our study had several limitations. First, survival bias may have impact on our observed associations and generalizability of the study results. It is possible that the association observed based on responded patients were biased towards patients with early stages of liver cancer who were generally under better medical conditions. This might limit the generalizability of the conclusion to all liver cancer population and in addition, the magnitude and direction of the survival selection bias could not be accurately estimated. However, because both HBV and family history are well established risk factors for liver cancer, there is a high possibility that the observed associations and interactions based on early stage patients might be underestimated. Second, as a case-control study, some of the exposure histories were collected through self-report, requiring participants to recall exposures that may have happened decades prior to the interview. However, because that the serological markers for HBV and HCV were measured in laboratory, and that family history of cancer is a striking memory in daily life for people, recall bias may not have strong impact on the major findings of the study. Also, the exposures to AFB_1 or microcystin contaminant were measured by self-reported history of mildew-contaminated food in-take or

raw water drinking instead of laboratory tests. These may weaken the ability to detect a more accurate association. Although the blood samples were collected after diagnoses of liver cancer among cases, according to the clinical data collected, few of the patients were receiving antiviral treatments for HBV/HCV infection. The possibility that the serological markers affected by treatment would be low.

In conclusion, this study detected a synergistic effect of family history and HBV infection on liver cancer risk, and reported the risk stratified by combinations of HBV sero-markers, HBV DNA levels together with family history of liver cancer, which can be employed to identify high-risk individuals for hepatitis treatment and liver cancer prevention more precisely.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

AFB_1	aflatoxin B_1
BMI	body mass index
CI	confidence interval
ELISA	enzyme-linked immunosorbent assay
HBcAb	hepatitis B core antibody
HBeAb	hepatitis B e antibody
HBeAg	hepatitis B e antigen
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV-Ab	hepatitis C virus antibody

OR	odds ratio
PCR	polymerase chain reaction
RR	risk ratio

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Keypoints

- Family history of liver cancer and hepatitis B are both risk factors of liver cancer.
- However, those infected with Hepatitis B Virus and have family history of liver cancer are at even higher risk of developing liver cancer.
- Treatment and close monitor of the hepatitis progression are especially important for these people.

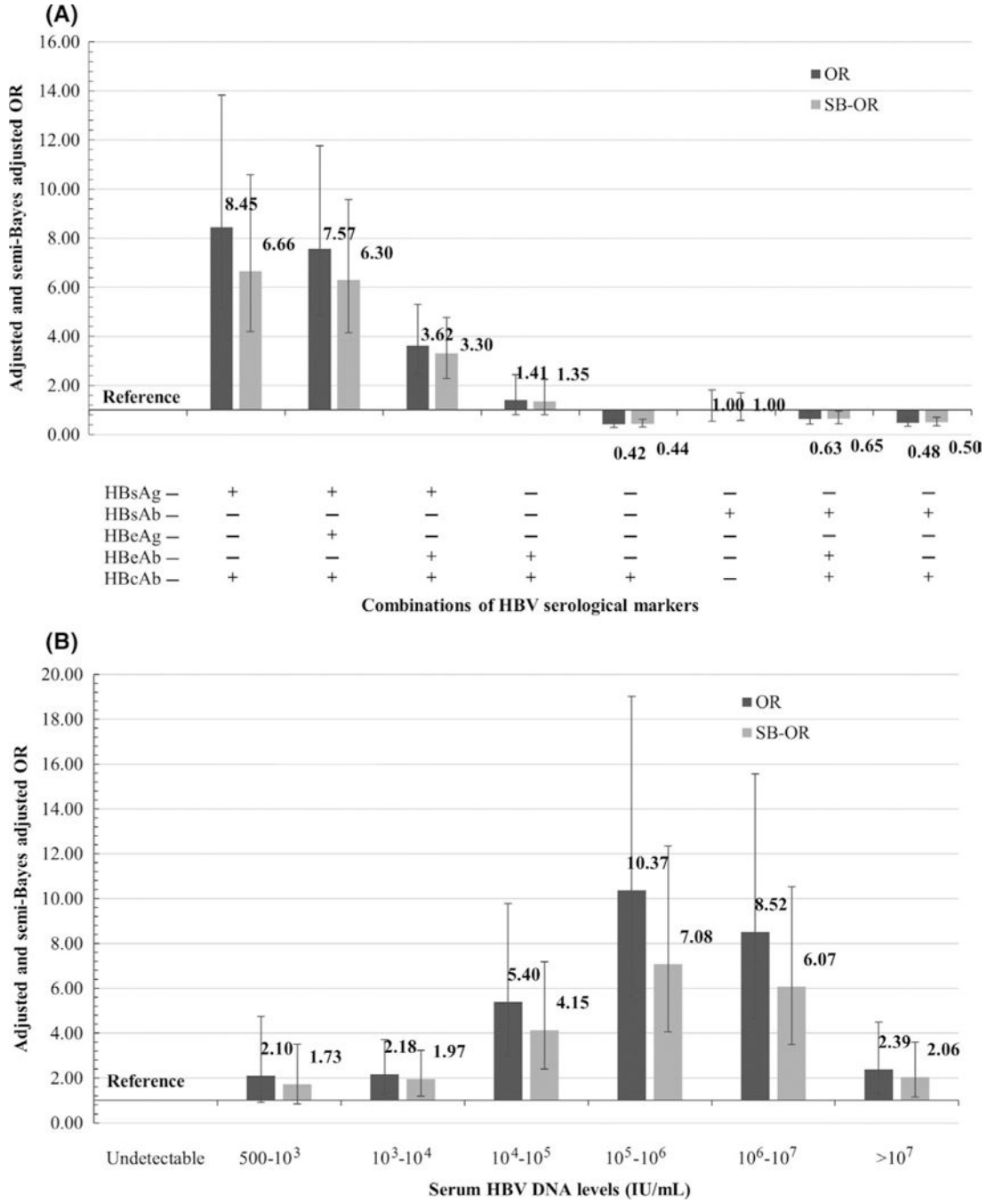

FIGURE 1.

(A) Adjusted and semi-Bayes adjusted ORs (95% CI) between HBsAg, HBsAb, HBeAg, HBeAb and HBcAb serostatus and liver cancer risk. (B) Adjusted and semi-Bayes adjusted ORs (95% CI) between serum HBV DNA levels and liver cancer risk. Prior OR: 1.00 (95% CI: 0.25–4.00). CI, confidence interval; HBcAb, hepatitis B core antibody; HBeAb, hepatitis B e antibody; HBeAg, hepatitis B e antigen; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; OR, odds ratio; SB-OR, semi- Bayes adjusted OR

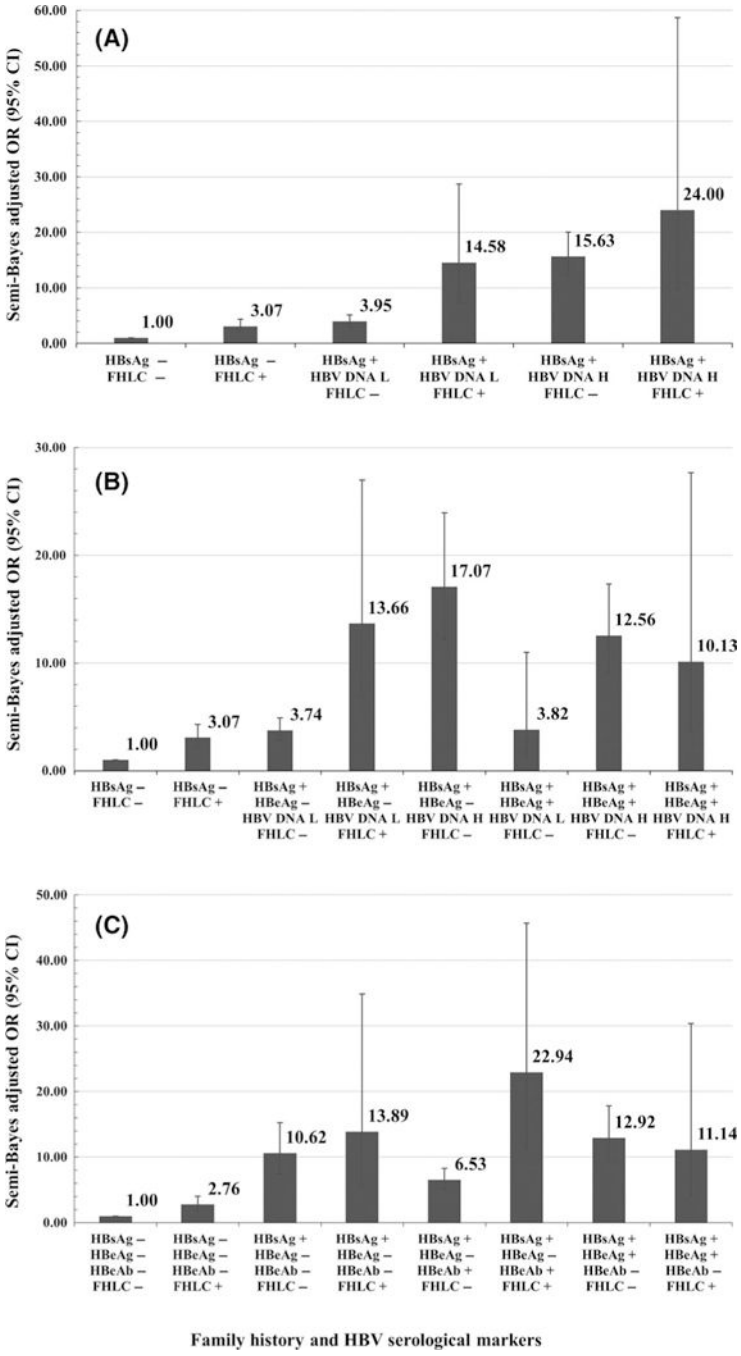

FIGURE 2.

(A) Family history of liver cancer, HBsAg serostatus, HBV DNA level and risk of liver cancer. (B) Family history of liver cancer, HBsAg, HBeAg, HBV DNA level and risk of liver cancer.(C) Family history of liver cancer, HBsAg, HBeAg, HBeAb and risk of liver cancer. HBV DNA L: low, less than 10000 IU/mL; H: high, greater than 10000 IU/mL. Prior OR: 1.00 (95% CI: 0.25–4.00). CI, confidence interval; HBeAb, hepatitis B e antibody; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; OR, odds ratio

TABLE 1

Socio-demographic characteristics of the subjects in Jiangsu liver cancer study (2003–2010; N = 9944)

Characteristics	Total	%	Case	%	Control	%	*P*-value
Total	9944		2011		7933		
County of residence							
Dafeng	3166	31.8	632	31.4	2534	31.9	<0.001
Ganyu	2400	24.1	390	19.4	2010	25.3	
Chuzhou	1435	14.4	301	15.0	1134	14.3	
Tongshan	2943	29.6	688	34.2	2255	28.4	
Gender							
Male	7239	72.8	1534	76.3	5705	71.9	<0.001
Female	2705	27.2	477	23.7	2228	28.1	
Age group (years)							
<50	1343	13.5	471	23.4	872	11.0	<0.001
50–59	2376	23.9	603	30.0	1773	22.4	
60–69	3057	30.7	515	25.6	2542	32.0	
70–79	2490	25.0	322	16.0	2168	27.3	
80-	678	6.8	100	5.0	578	7.3	
Marital Status							
In marriage	8143	82.4	1717	86.0	6426	81.5	<0.001
Single, divorced or widowed	1742	17.6	279	14.0	1463	18.5	
Missing	59		15		44		
Education level							
Illiteracy	4560	46.0	764	38.2	3796	48.0	<0.001
Primary	3152	31.8	662	33.1	2490	31.5	
Middle	1759	17.7	461	23.1	1298	16.4	
High	393	4.0	101	5.1	292	3.7	
College	52	0.5	12	0.6	40	0.5	
Missing	28		11		17		
Per capita family income 10 y ago (RMB yuan/year)							
<1000	2048	21.1	392	20.0	1656	21.3	0.119
1000-	1917	19.7	405	20.6	1512	19.5	

Characteristics	Total	%	Case	%	Control	%	P-value
1500-	2544	26.1	487	24.8	2057	26.5	
2500-	3222	33.1	680	34.6	2542	32.7	
Missing	213		47		166		
BMI							
<23.0	5475	55.5	1290	65.2	4185	53.0	<0.001
23.0-	3729	37.8	603	60.5	3126	39.6	
27.5-	530	5.4	56	2.8	474	6.0	
32.5-	32	0.3	7	0.4	25	0.3	
37.5	104	1.1	24	1.2	80	1.0	
Missing	74		31		43		
Ever smoke							
No	5212	52.4	971	48.3	4241	53.5	<0.001
Yes	4732	47.6	1040	51.7	3692	46.5	
Ever drink							
No	5139	51.7	885	44.0	4254	53.6	<0.001
Yes	4805	48.3	1126	56.0	3679	46.4	
Have family history of liver cancer							
No	9419	94.7	1735	86.3	7684	96.9	<0.001
Yes	525	5.3	276	13.7	249	3.1	

Abbeviations: BMI, body mass index.

TABLE 2

The association between major risk factors and liver cancer in Jiangsu Study, 2003-2010

Variables	Number and proportion (%) of positive by case/control	Adjusted OR[a] (95% CI)*	Semi-Bayes posterior OR (95% PI) with 4 sets of priors			
			Informative (see below)	1(1/2,2)	1 (1/4–4)	1 (1/16,16)
Total	2011/7933					
Family history of liver cancer			*3.49 (2.68–4.53)*[b]			
Overall	276(13.7)/249(3.1)	**4.32 (3.25–5.73)**	**3.85 (3.18–4.67)**	**3.50(2.69–4.55)**	**4.07 (3.09–5.38)**	**4.26 (3.21–5.64)**
Male	216(14.1)/181(3.2)	**4.71 (3.35–6.63)**	**3.90 (3.17–4.80)**	**3.48 (2.56–4.73)**	**4.31 (3.09–6.00)**	**4.60 (3.28–6.46)**
Female	60(12.6)/68(3.1)	**3.67 (2.16–6.23)**	**3.52 (2.79–4.46)**	**2.27 (1.49–3.46)**	**3.11 (1.90–5.10)**	**3.51 (2.08–5.90)**
Family history of liver cancer in first-degree relatives			*3.49 (2.68–4.53)*			
Overall	232(11.5)/161(2.0)	**5.12 (3.71–7.07)**	**4.07 (3.32–4.98)**	**3.83 (2.86–5.13)**	**4.71 (3.44–6.45)**	**5.01 (3.64–6.90)**
Male	184(12.0)/127(2.2)	**5.32 (3.64–7.76)**	**4.00 (3.23–4.97)**	**3.62 (2.60–5.05)**	**4.74 (3.29–6.83)**	**5.16 (3.55–7.51)**
Female	48(10.1)/34(1.5)	**5.02 (2.64–9.55)**	**3.68 (2.88–4.69)**	**2.38 (1.49–3.81)**	**3.77 (2.11–6.76)**	**4.62 (2.47–8.65)**
HBsAg-positive (1211 cases and 6478 controls have serum sample)			*11.34(8.72–14.75)*			
Overall	524(43.2)/425(6.6)	**9.94 (8.33–11.87)**	**10.36 (8.94–12.00)**	**8.64 (7.27–10.25)**	**9.58 (8.04–11.42)**	**9.85 (8.25–11.75)**
Male	429(46.6)/315(6.8)	**11.15 (9.04–13.76)**	**11.22 (9.53–13.23)**	**9.10 (7.45–11.13)**	**10.56 (8.58–13.00)**	**11.00 (8.92–13.56)**
Female	95(32.6)/110(5.9)	**7.35 (5.20–10.39)**	**9.68 (7.85–11.93)**	**4.94 (3.62–6.73)**	**6.54 (4.67–9.15)**	**7.13 (5.06–10.05)**
Anti-HCV-positive (1211 cases and 6478 controls have serum sample)			*4.28 (3.30–5.56)*			
Overall	ll(0.9)/53(0.8)	1.36(0.61–3.06)	**3.84 (3.00–4.92)**	1.14 (0.67–1.93)	1.26(0.63–2.53)	1.33 (0.61–2.88)
Male	8(0.9)/40(0.9)	1.47 (0.55–3.98)	**3.99 (3.10–5.14)**	1.14 (0.64–2.00)	1.29(0.58–2.89)	1.41 (0.55–3.57)
Female	3(1.0)/13(0.7)	1.27(0.32–5.09)	**4.11 (3.18–5.30)**	1.05(0.56–1.95)	1.13 (0.42–3.00)	1.21(0.35–4.18)
History of mildew-contaminated food intake			*1.80(1.44–2.25)*			
Overall	219(10.9)/646(8.1)	1.17(0.89–1.54)	**1.52 (1.28–1.80)**	1.15 (0.89–1.48)	1.16(0.89–1.52)	1.17(0.89–1.53)
Male	174(11.3)/454(8.0)	1.00 (0.71–1.40)	**1.51 (1.25–1.82)**	1.00 (0.74–1.36)	1.00 (0.72–1.39)	1.00 (0.71–1.40)
Female	45(9.4)7192(8.6)	1.54 (0.95–2.49)	**1.75 (1.43–2.14)**	1.34 (0.90–1.99)	1.47 (0.93–2.32)	1.52 (0.95–2.44)
History of raw water intake			*1.77(1.09-2.87)*			
Overall	1238(61.6)/4216(53.1)	**1.33 (1.13–1.55)**	**1.37 (1.18–1.59)**	**1.31 (1.12–1.53)**	**1.33 (1.13–1.55)**	**1.33 (1.13–1.56)**
Male	973(63.4)/3036(53.2)	**1.39 (1.15–1.68)**	**1.44 (1.20–1.71)**	**1.36 (1.13–1.63)**	**1.38 (1.15–1.67)**	**1.39 (1.15–1.68)**
Female	265(55.6)/1180(53.0)	1.14 (0.85–1.52)	**1.28 (1.00–1.64)**	1.12 (0.86–1.46)	1.13 (0.85–1.51)	1.14 (0.85–1.52)

[a] Abbevlatlons: BMI, body mass index; Cl, confidence interval; HCV, hepatitis C virus; HbsAG, hepatitis B surface antigen; OR, odds ratio.

Adjusted for age (continuous), gender (male = 0, female = 1), education level (Illiteracy = 0, primary = 1, middle = 2, high school or college = 3, entered as dummy variable), marital status (In marriage = 1, single, divorced or widowed = 0), per capita family Income 10 y ago (Yuan/year, continuous), BMI (continuous), family history of liver cancer (yes = 1, no = 0), pack-year of smoking (continuous), weekly ethanol consumption in 1990s (mL/week, continuous), history of mlldew-contamlnated food Intake (yes = 1, no = 0), history of raw water drinking (yes = 1, no = 0), HBsAg status (positive = 1, negative = 0, except for variable of HBsAg status), anti-HCV status (positive = 1, negative = 0, except for variable of antl-HCV status) and county of residence (Dafeng = 1, Ganyu = 2, Chuzhou = 3, Tongshan = 4, entered as dummy variable).

[b] ORs In Bolds were extracted from the meta-analysis and used as priors In this analysis.[8]

[*] Estlmates In bold showed $P < 0.05$

TABLE 3

The distribution of HBV marker combinations and the association between common combinations and liver cancer in the Jiangsu Study (2003-2010; N = 7689)

Status of HBV markers (negative = 0, positive = 1)									
HBsAg	**HBsAb**	**HBeAg**	**HBeAb**	**HBcAb**	**Case (%)**	**Control (%)**	**Crude OR (95% Cl)***	**Adjusted OR[a] (95% Cl)**	**Semi-Bayes Posterior OR (95% PI), prior: 1 (1/4, 4)**
0	0	0	0	0	59 (4.9)	324 (5.0)	1.00	1.00	1.00
0	0	0	0	1	172 (14.2)	2017(31.1)	**0.47 (0.34–0.64)**	**0.42 (0.29–0.60)**	**0.44 (0.31–0.63)**
0	0	0	1	1	32 (2.6)	115(1.8)	1.53 (0.95–2.47)	1.41 (0.81–2.44)	1.35 (0.81–2.25)
0	1	0	0	0	23 (1.9)	102 (1.6)	1.24 (0.73–2.11)	1.00 (0.55–1.82)	1.00(0.58–1.73)
0	1	0	1	1	86 (7.1)	567 (8.8)	0.83 (0.58–1.19)	**0.63 (0.42–0.94)**	**0.65 (0.44–0.96)**
1	0	0	0	1	121 (10.0)	54 (0.8)	**12.31 (8.05–18.80)**	**8.45 (5.16–13.82)**	**6.66 (4.19–10.58)**
0	1	0	0	1	312 (25.8)	2903 (44.8)	**0.59 (0.44–0.80)**	**0.48 (0.34–0.67)**	**0.50 (0.36–0.70)**
1	0	0	1	1	208 (17.2)	261 (4.0)	**4.38 (3.14–6.10)**	**3.62 (2.47–5.31)**	**3.30(2.29–4.78)**
1	0	1	0	1	151 (12.5)	81(1.3)	**10.24(6.95–15.08)**	**7.57 (4.87–11.77)**	**6.30(4.15–9.57)**
1	0	0	0	0	7 (0.6)	3(0.1)			
1	0	0	1	0	9 (0.7)	3(0.1)			
1	0	1	0	0	3 (0.3)	0			
1	0	1	1	1	8 (0.7)	1 (0.0)			
1	1	0	0	0	2 (0.2)	0			
1	1	0	0	1	1 (0.1)	12 (0.2)			
1	1	0	1	1	3(0.3)	6(0.1)			
1	1	1	0	1	10 (0.8)	2 (0.0)			
0	0	1	0	0	1 (0.1)	6(0.1)			
0	0	1	0	1	1 (0.1)	3(0.1)			
0	1	0	1	0	1 (0.1)	1 (0.0)			
0	1	1	0	0	0	2 (0.0)			
0	1	1	0	1	1 (0.1)	12 (0.2)			
0	0	0	1	0	0	3(0.1)			

Adjusted for age (continuous), gender (male = 0, female = 1), education level (illiteracy = 0, primary = 1, middle = 2, high school or college = 3, entered as dummy variable), marital status (in marriage = 1, single, divorced or widowed = 0), per capita family income 10 y ago (Yuan/year, continuous), BMI (continuous), family history of liver cancer (yes = 1, no = 0), pack-year of smoking (continuous), weekly ethanol consumption in 1990s (mL/week, continuous), history of mildew-contaminated food intake (yes = 1, no = 0), history of raw water drinking (yes = 1, no = 0), anti-HCV status (positive = 1, negative = 0) and county of residence (Dafeng = 1, Ganyu = 2, Chuzhou = 3, Tongshan = 4, entered as dummy variable).

Abbeviations: BMI, body mass index; CI, confidence interval; HBV, hepatitis B virus; HBcAb, hepatitis B core antibody; HBeAb, hepatitis B e antibody; HBeAg, hepatitis B e antigen; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen.

*Estimates in bold showed $P < 0.05$.

TABLE 4

The association between serum HBV DNA level with risk of liver cancer among the HBsAg-positive participants in Jiangsu Study (2003–2010; N = 915)

HBV Viral Load (VL)	Cases	%	Controls	%	Crude OR (95% CI)*	Adjusted OR[a] (95% CI)	Semi-Bayes Posterior OR (95% PI) With prior: 1 (1/4, 4)
One log increase in HBV viral load					**1.21 (1.09–1.34)**	**1.17 (1.03–1.32)**	**1.17 (1.03–1.32)**
Tertile					$P_{\text{for trend}} < 0.001$	$P_{\text{for trend}} < 0.001$	
Undetectable	56	11.3	158	37.6	1.00	1.00	1.00
Tertile 1	57	11.5	87	20.7	**1.85 (1.18–2.91)**	**1.83 (1.06–3.16)**	**1.69 (1.02–2.80)**
Tertile 2	199	40.2	87	20.7	**6.45 (4.35–9.58)**	**6.37 (3.92–10.34)**	**5.21 (3.30–8.23)**
Tertile 3	183	37.0	88	21.0	**5.87 (3.95–8.73)**	**5.21 (3.20–8.49)**	**4.34 (2.74–6.88)**
VL group (IU/mL)					$P_{\text{for trend}} < 0.001$	$P_{\text{for trend}} < 0.001$	
Undetectable	56	11.3	158	37.6	1.00	1.00	1.00
500–10^3	17	3.4	30	7.1	1.60 (0.82–3.12)	2.10 (0.92–4.76)	1.73 (0.85–3.51)
10^3-10^4	69	13.9	79	18.8	**2.46 (1.58–3.84)**	**2.18 (1.27–3.72)**	**1.97 (1.19–3.25)**
10^4-10^5	85	17.2	43	10.2	**5.58 (3.46–8.99)**	**5.40 (2.98–9.79)**	**4.15 (2.41–7.18)**
10^5-10^6	112	22.6	33	7.9	**9.58 (5.85–15.69)**	**10.37 (5.65–19.01)**	**7.08 (4.06–12.34)**
10^6-10^7	109	22.0	29	6.9	**10.61 (6.37–17.67)**	**8.52 (4.66–15.57)**	**6.07 (3.50–10.54)**
≥10^7	47	9.5	48	11.4	**2.76 (1.67–4.58)**	**2.39 (1.27–4.50)**	**2.06 (1.16–3.60)**

Abbeviations: BMI, body mass index; CI, confidence interval; HBV, hepatitis B virus; HbsAG, hepatitis B surface antigen; OR, odds ratio.

Adjusted for age (continuous), gender (male = 0, female = 1), education level (illiteracy = 0, primary = 1, middle = 2, high school or college = 3, entered as dummy variable), marital status (in marriage = 1, single, divorced or widowed = 0), per capita family income 10 y ago (Yuan/year, continuous), BMI (continuous), family history of liver cancer (yes = 1, no = 0), pack-year of smoking (continuous), weekly ethanol consumption in 1990s (mL/week, continuous), history of mildew-contaminated food intake (yes = 1, no = 0), history of raw water drinking (yes = 1, no = 0), anti-HCV status (positive = 1, negative = 0) and county of residence (Dafeng = 1, Ganyu = 2, Chuzhou = 3, Tongshan = 4, entered as dummy variable).

*Estimates in bold showed $P < 0.05$.

TABLE 5

Family history of liver cancer, HBsAg, HBeAg, HBeAb status, high HBV DNA level and liver cancer risk in Jiangsu study, 2003-2010

Characteristics	Case/ctrl	Adjusted OR[a] (95% CI)*	SB-Adjusted OR (95% PI)
HBsAg/HBV DNA > 10000 IU/mL/Family history			
0/-/0	637/5881	1.00	1.00
0/-/1	52/193	**3.30 (2.32–4.70)**	**3.07 (2.18–4.32)**
1/0/0	116/249	**4.16 (3.18–5.45)**	**3.95 (3.03–5.15)**
1/0/1	26/13	**33.86 (15.56–73.67)**	**14.58 (7.40–28.72)**
1/1/0	272/148	**17.10 (13.31–21.98)**	**15.63 (12.21–20.00)**
1/1/1	81/5	**233.88 (72. 34–756.17)**	**24.00 (9.80–58.76)**
HBsAg/HBeAg/HBV DNA > 10000 IU/mL/Family history			
0/-/-/0	637/5881	1.00	1.00
0/-/-/1	52/193	**3.30 (2.32–4.69)**	**3.07 (2.18–4.32)**
1/0/0/0	108/246	**3.94 (3.00–5.19)**	**3.74 (2.86–4.90)**
1/0/0/1	25/13	**31.33 (14.35–68.43)**	**13.66 (6.92–26.98)**
1/0/1/0	145/70	**20.44 (14.42–28.99)**	**17.07 (12.17–23.95)**
1/0/1/1	49/2	NA	NA
1/1/0/0	8/2	**24.03 (4.74–121.89)**	**3.82 (1.33–10.97)**
1/1/0/1	1/0	NA	NA
1/1/1/0	127/78	**14.52 (10. 42–20.23)**	**12.56 (9.10–17.34)**
1/1/1/1	32/3	**130.21 (30. 37–558.24)**	**10.13 (3.71–27.65)**
HBsAg/HBeAg/HBeAb/Family history			
0/0/0/0	527/5195	1.00	1.00
0/0/0/1	39/165	**3.00 (2.01–4.47)**	**2.76 (1.88–4.05)**
1/0/0/0	102/66	**12.65 (8.68–18. 46)**	**10.62 (7.38–15.28)**
1/0/0/1	29/3	**111.42 (32.46–382.52)**	**13.89 (5.53–34.89)**
1/0/1/0	173/259	**6.93 (5. 42–8.86)**	**6.53 (5.13–8.32)**
1/0/1/1	48/12	**64.23 (29.01–142.21)**	**22.94 (11.51–45.70)**
1/1/0/0	130/80	**14.95 (10.73–20.82)**	**12.92 (9.36–17.83)**
1/1/0/1	34/3	**158.73 (37.04–680.28)**	**11.14 (4.08–30.40)**

Abbeviations: BMI, body mass index; CI, confidence interval; HBV, hepatitis B virus; HBeAb, hepatitis B e antibody; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; OR, odds ratio.

Adjusted for age (continuous), gender (male = 0, female = 1), education level (illiteracy = 0, primary = 1, middle = 2, high school or college = 3, entered as dummy variable), marital status (in marriage = 1, single, divorced or widowed = 0), per capita family income 10 y ago (Yuan/year, continuous), BMI (continuous), family history of liver cancer (yes = 1, no = 0), pack-year of smoking (continuous), weekly ethanol consumption in 1990s (mL/week, continuous), history of mildew-contaminated food intake (yes = 1, no = 0), history of raw water drinking (yes = 1, no = 0), anti-HCV status (positive = 1, negative = 0) and county of residence (Dafeng = 1, Ganyu = 2, Chuzhou = 3, Tongshan = 4, entered as dummy variable), except when the variable itself is being examined.

*Estimates in bold showed $P < 0.05$.

TABLE 6

Interaction on additive and multiplicative scale between HBsAg-positive, HBeAg-positive, and HBV DNA > 1000. and liver cancer in Jiangsu study, 2003–2010

			Adjusted OR[a]	SB-Adjusted OR	Interaction	
Factors		**case/control**	**(95% CI)***	**(95% PI)**	**(95% CI)**	
Family history of liver cancer/HBsAg-positive						
No	No	637/5881	1.00	1.00	ROR	**2.84 (1.41–5.75)**
No	Yes	412/407	**9.14 (7.60–11.00)**	**8.79 (7.32–10.56)**	RERI	**73.13 (21.96–124.30)**
Yes	No	52/193	**3.25 (2.29–4.62)**	**3.03 (2.15–4.25)**	AP	**0.87 (0.78–0.95)**
Yes	Yes	112/18	**84.53 (46.03–155.22)**	**41.34 (23.69–72.12)**	S	**8.04 (4.29–15.04)**
Family history of liver cancer/HBeAg-positive						
No	No	910/6197	1.00	1.00	ROR	2.40 (0.54–10.76)
No	Yes	139/106	**8.63 (6.40–11.64)**	**7.85 (5.86–10.51)**	RERI	**91.96 (−60.10–244.02)**
Yes	No	128/210	**5.04 (3.86–6.59)**	**4.76 (3.66–6.19)**	AP	**0.88 (0.70–1.06)**
Yes	Yes	36/3	**104.64 (24.45–447.76)**	**9.16 (3.36–24.98)**	S	**8.88 (2.01–39.10)**
Family history of liver cancer/HBV DNA > 10000 IU/mL						
No	No	116/254	1.00	1.00	ROR	1.66 (0.38–7.29)
No	Yes	272/148	**4.03 (2.82–5.77)**	**3.70 (2.61–5.23)**	RERI	27.09 (−15.85 to 70.04)
Yes	No	26/13	**5.29 (2.24–12.52)**	**3.33 (1.60–6.92)**	AP	**0.76 (0.46–1.07)**
Yes	Yes	81/5	**35.42 (10.45–120.04)**	**7.46 (2.98–18.65)**	S	**4.70 (1.20–18.35)**

Abbeviations: BMI, body mass index; CI, confidence interval; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; OR, odds ratio.

Adjusted for age (continuous), gender (male = 0, female = 1), education level (illiteracy = 0, primary = 1, middle = 2, high school or college = 3, entered as dummy variable), marital status (in marriage = 1, single, divorced or widowed = 0), per capita family income 10 y ago (Yuan/year, continuous), BMI (continuous), family history of liver cancer (yes = 1, no = 0), pack-year of smoking (continuous), weekly ethanol consumption in 1990s (mL/week, continuous), history of mildew-contaminated food intake (yes = 1, no = 0), history of raw water drinking (yes = 1, no = 0), anti-HCV status (positive = 1, negative = 0) and county of residence (Dafeng = 1, Ganyu = 2, Chuzhou = 3, Tongshan = 4, entered as dummy variable), except when the variable itself is being examined.

*Estimates in bold showed $P < 0.05$.