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Additive interaction between hepatitis B virus infection and tobacco smoking on the risk of gastric cancer in a Chinese population

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Abstract

Objective Although hepatitis B virus (HBV) infection was regarded as a risk factor for liver cancer, the association of HBV infection with gastric cancer (GC) is unclear. In this study, we aim to assess the association of HBV infection with the risk of GC and explore the interaction between HBV infection and other risk factors.

Methods A case-control study was conducted and 409 GC cases and 1275 healthy controls were enrolled in Fujian province, China. Serum hepatitis B surface antigen (HBsAg) was measured and epidemiological data were collected. The association between HBV infection and GC risk was analyzed using logistic regression and meta-analysis method was employed to make estimates more conservative. Meanwhile, multiplicative and additive models were used to explore the interaction between HBV infection and other risk factors.

Results The prevalence of serum HBsAg positivity was 13.20% among GC cases and 6.20% among controls. Compared to HBsAg-negative subjects, the adjusted odds ratios (*OR*) for HBsAg positive were 3.30 [95% confidence interval (*CI*): (1.84–5.91)]. Compared to HBsAg-negative never smokers, the adjusted *OR* was 2.00 (95%*CI*: 1.19–3.34) for HBsAg-negative ever smokers,4.27 (95%*CI*: 1.97–9.26) for HBsAg-positive never smokers, and 4.73 (95%*CI*: 1.85–12.08) for HBsAg-positive ever smokers. These evidences indicated super-additive [API (95%*CI*): 0.78 (0.67–0.90), S (95%*CI*): 5.45 (3.26–9.08)] between HBV infection and tobacco smoking. No interaction between HBV infection and alcohol drinking was found on the risk of GC.

Conclusions HBV infection increased the risk of GC, and tobacco smoking and HBV infection may positively interact in the development of GC.

Keywords Hepatitis B, Gastric cancer, Case-control study, Meta-analysis, Interaction

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Introduction

According to the latest data from the International Agency for Research on Cancer, gastric cancer (GC) is the fifth most common cancer and the fourth most deadly cancer worldwide [1]. Identified risk factors such as unhealthy eating patterns, a familial predisposition to cancer, and infections caused by viruses like Epstein-Barr virus (EBV), Helicobacter pylori (HP), and human papillomavirus, have been linked to the onset of GC [2]. However, the traditional risk factors for GC do not fully explain the current incidence of GC in the general population.

In 2012, the United States Food and Drug Administration (FDA) compiled a comprehensive list of dangerous and potentially harmful ingredients present in both unburned tobacco and tobacco smoke, among which 11 substances were categorized as Group 1 carcinogens for humans by the International Agency for Research on Cancer (IARC) [3]. Smoke and tar from tobacco combustion contain polycyclic aromatic hydrocarbons (PAHs), benzo(a)pyrene, nitroso compounds and other carcinogens [4, 5]. These harmful substances not only induce lung and upper respiratory tract cancers, but also lead to cancers of the digestive tract and other organs, including esophagus, stomach, pancreas and lower urinary tract cancers [3], especially gastric cancer. Carcinogenic substances in cigarette smoke will enter the stomach with saliva and directly stimulate the gastric mucosa, causing submucosal vasoconstriction, spasm, ischemia and hypoxia of the gastric mucosa, which promotes the occurrence of gastritis and gastric ulcers and slows down their healing, leading to precancerous lesions [6, 7].

The International Agency for Research on Cancer (IARC) Monograph Program has consistently recognized alcohol as a Group 1 carcinogen [8]. Some studies have shown that alcohol consumption increases the risk of oral, esophageal, liver, colorectal, and breast cancers in women [9]. However, for GC, the evidence related to alcohol consumption is still limited and a weak dose-risk association has been observed [10]. It is worth noting that alcohol can make neutrophils infiltrate the gastric mucosa and release myeloperoxidase (MPO), oxygen free radicals, reactive oxygen species (ROS) metabolites such as superoxide anion, protease, etc., prompting the occlusion of the large blood vessels, which leads to inflammation and damage of gastric mucosa [11, 12]. Meanwhile, alcohol can change the gastric environment and accelerate the absorption of carcinogenic substances and carcinogens, such as nitrosamines, mycotoxins, polycyclic aromatic hydrocarbons [13].

With the development of "inflammation-cancer" translational research, the impact of hepatitis B virus (HBV) infection on cancer has received increasing attention [14]. Chronic hepatitis B virus infection is a major susceptibility factor for cirrhosis, liver failure and hepatocellular carcinoma [15]. In recent years, there is increasing evidence that HBV can be detected in extrahepatic organ tissues, suggesting that HBV may play an important role in extrahepatic tumorigenesis [16–18]. The mechanisms of HBV carcinogenesis may include direct and indirect mechanisms. Direct mechanisms are manifested by the integration of HBV DNA into the host genome, altering host gene expression and signaling pathways [19]. Indirect mechanisms involve chronic hepatitis B virus infection associated with persistent inflammation, hypoxia, angiogenesis and oxidative stress, all of which may play a role in causing cancer [19].

Available studies have shown clinical signs of comorbidity between HBV and GC. Some researchers have evaluated the association between HBV infection and GC, but the findings are not yet fully consistent. For example, the results of a hospital-based case-control study in the Jiangsu region by Cui [20] et al. showed no association between HBV infection and GC risk. However, a nested case-control study of a population-based cohort in Changzhou City, Jiangsu Province, found that HBV infection may increase the risk of GC (*OR*: 1.76, 95%*CI*: 1.04–2.98) [21]. In addition, the results of a study in the United States of America on elderly people showed that HBV infection was associated with a high risk of GC (*OR*: 1.19, 95%*CI*: 1.03–1.37) [22]. Based on this, a meta-analysis of the association between HBV infection and the risk of gastric cancer was conducted in the pre-study phase of this study. It was found that there was a positive correlation between the two [23]. The inconsistency of these results may be related to the complex etiology of GC, differences in genetic background and environmental exposures, and variations in the prevalence of HBV infection among populations of different ethnicities and regions. Fujian Province has a high incidence of gastric cancer and also a high incidence of HBV infection. However, there has been no study on the association between the two. Therefore, the association between HBV infection and GC in the Fujian Province population remains to be explored.

In this study, a hospital-based case-control study was conducted to explore the association between HBV infection and GC and further assessed the interaction between HBV infection, smoking, and alcohol consumption on the risk of GC.

Methods

Study subjects and design

Patients with GC diagnosed pathologically between September 2019 and June 2023 at the First Affiliated Hospital of Fujian Medical University and Fujian Provincial Cancer Hospital were included in this study. The inclusion criteria for cases were: [1] new patients with primary

gastric cancer confirmed by pathology; [2] complete clinical data; and [3] being of Fujian origin or living in Fujian for more than 10 years. The inclusion criteria for control were: [1] no history of tumor disease; [2] being of Fujian origin or living in Fujian for more than 10 years. The exclusion criteria for the study subjects were: [1] psychiatric patients, or those for whom epidemiological data could not be investigated; [2] history of other malignant tumors or cases of cancer metastasis to gastric cancer; and [3] incomplete basic information or clinical data.

Data collection and measure

A uniformly developed structured questionnaire was used to interview the study participants. The questionnaire included [1] socio-demographic characteristics: general situation, occupational history, family situation and socio-economic status, etc.; [2] health-related behavioral patterns: history of smoking, alcohol and tea consumption, dietary history, reproductive history (for females only), physical activity, etc.; and [3] personal history: personal health status, history of hypertension, diabetes mellitus, history of medications, family history, mental sleep and emotional status, oral hygiene, etc. The investigations were all about information and data related to the study subjects before the onset of the disease. Fasting venous blood of 3–5 ml was collected from each subject using a vacuum blood collection needle assembly, EDTA anticoagulated vacuum tubes and non-anticoagulated vacuum tubes. The blood samples were also centrifuged to obtain serum, plasma, leukocytes and erythrocytes within 4 h of sampling, which were packed into separate cryopreservation tubes and stored frozen below − 20℃. Each participant recruited for this study received a blood test for HBV infection at the first visit as part of the routine examination. Blood test results were collected retrospectively from medical records. HBV infection was defined in this study as serum Hepatitis B surface antigen (HBsAg) positivity.

Statistical analyses

The chi-square test was used to assess the differences between the case and control groups in terms of demographic characteristics and clinical parameters. Unconditional logistic regression models were used to estimate the *OR* and 95%*CI* of the ratio of HBV infection to the risk of GC and to adjust for different confounders by fitting multiple models. Multiplicative and additive interactions of HBV infection with smoking and alcohol consumption were analyzed separately using multivariate logistic regression models. The *OR* and its 95%*CI* were used to evaluate the multiplicative interaction effect, and a multiplicative interaction effect was indicated when the 95%*CI* of the *OR* did not contain 1. Calculated measures of additive interaction effects included: relative excess risk of interaction (RERI), attributable proportion of interaction (API), and synergy index (S). It was calculated according to the following formulas: $\mathrm{RERI} = OR_{11}\text{-}OR_{10}\text{-}OR_{01} + 1$, $\mathrm{API} = \mathrm{RERI}/OR_{11}$, and $\mathrm{S}=(OR_{11}\text{-}1)/[(OR_{10}\text{-}1)+(OR_{01}\text{-}1)]$. An additive interaction effect between the two factors was indicated if the confidence intervals for RERI and API did not contain 0 and the confidence interval for S did not contain 1. In addition, some sensitivity analyses were performed. Subgroup analyses were performed to explore the association between HBV infection and GC in specific populations. E-values were calculated to assess potential residual confounding by unmeasured factors. Statistical analyses were performed using R (V.4.2.1, R Foundation) software and Stata 17.0 software. All *P* values were based on two-sided tests and $P < 0.05$ was considered statistically significant.

Results

Demographic characteristics

A total of 409 GC case subjects and 1275 healthy control subjects were included in this study, of which 58.7% were male. Table 1 shows the distribution of demographics, socioeconomic characteristics, and lifestyle behaviors of the case and control groups. The case group tended to be more often older men, and the two groups also differed in terms of marital status, education level, income, BMI, smoke, drink and tea consumption, history of diabetes, and history of hypertension ($P < 0.05$).

Association between HBV infection and GC

As shown in Table 2, the *OR* of the risk of gastric cancer in HBV-infected individuals was 2.30 (95%*CI*: 1.60–3.32) compared to HBV-uninfected individuals. The strength of association a*OR* (95%*CI*) between HBV infection and GC was 3.53 (2.05–6.06) after adjusting for sex and age in model 1. Based on model 1, model 2 added adjustment for general demographic information such as marital status, education level, and income, with an a*OR* (95%*CI*) of 3.36 (1.91–5.91). Model 3 further adjusted for BMI, smoking, alcohol, tea, taste, history of diabetes, and history of hypertension with an a*OR* (95%*CI*) of 3.30 (1.84–5.91).

Interaction of HBV with smoking and drinking

The multiplicative and additive interactions between HBV and smoking were analyzed in Tables 3 and 4, respectively. The additive interaction between HBV and smoking showed that the 95%*CI* for API excluding 0, the 95%*CI* for S excluding 1, and API > 0 and S > 1. This suggests that there may be an additive effect of combined exposure to HBV infection and smoking on the risk of GC, and that the fraction of the total effect attributable to the interaction was 78%. Compared to HBsAg-negative never smokers, the adjusted *OR* was 2.00 (95%*CI*:

Table 1 General characteristics of the study population

variables	Case (%) *n* = 409	Control (%) *n* = 1275	χ^2	*P*
Sex			36.067	< 0.001
Male	292(71.39)	696(54.59)		
Female	117(28.61)	579(45.41)		
Age			888.442	< 0.001
≤ 45	22(5.38)	788(61.80)		
46–59	92(22.49)	428(33.57)		
≥ 60	295(72.13)	59(4.63)		
Marital status			108.483	< 0.001
Unmarried	4(0.98)	220(17.25)		
Married	379(92.67)	1044(81.88)		
Other	26(6.36)	11(0.86)		
Education level			607.532	< 0.001
Primary and below	220(53.79)	76(5.96)		
Junior/Senior High School	159(38.88)	385(30.20)		
College and above	30(7.33)	814(63.84)		
Income			139.641	< 0.001
< 5000	92(22.49)	71(5.57)		
5000–10,000	156(38.14)	358(28.08)		
> 10,000	161(39.36)	846(66.35)		
BMI(kg/m^2)			16.151	< 0.001
< 18.5	43(10.51)	77(6.04)		
18.5–23.9	255(62.35)	744(58.35)		
≥ 24	111(27.14)	454(35.61)		
Smoke			52.429	< 0.001
Yes	199(48.66)	372(29.18)		
No	210(51.34)	903(70.82)		
Drink			32.516	< 0.001
Yes	112(27.38)	551(43.22)		
No	297(72.62)	724(56.78)		
Drinking tea			77.620	< 0.001
Yes	143(34.96)	764(59.92)		
No	266(65.04)	511(40.08)		
Taste			62.009	< 0.001
Insipid	60(14.67)	430(33.73)		
Normal	187(45.72)	521(40.86)		
Salty	162(39.61)	324(25.41)		
mealtime			3.694	0.158
Quick	153(37.41)	447(35.06)		
Normal	219(53.55)	741(58.12)		
Slow	37(9.05)	87(6.82)		
History of diabetes			108.495	< 0.001
Yes	64(15.65)	28(2.20)		
No	345(84.35)	1247(97.80)		
History of hypertension			149.416	< 0.001
Yes	113(27.63)	74(5.80)		
No	296(72.37)	1201(94.20)		

1.19–3.34) for HBsAg-negative ever smokers, 4.27 (95%*CI*: 1.97–9.26) for HBsAg-positive never smokers, and 4.73 (95%*CI*: 1.85–12.08) for HBsAg-positive ever smokers. In addition, the additive effect of smoking and HBV was 5.45 times than the sum of the independent effects of them. However, no multiplicative interaction was found between HBV infection and smoking on the prevalence of GC ($P > 0.05$).

The multiplicative and additive interactions between HBV and drinking were analyzed in Tables 5 and 4, respectively. The additive interaction between HBV and alcohol consumption showed that the 95%*CI* for RERI included 0, the 95%*CI* for API included 0, and the 95%*CI* for S included 1. This revealed that there might not be an additive interaction between HBV infection and alcohol consumption. Also, no multiplicative interaction was found between HBV infection and alcohol consumption on the prevalence of GC ($P > 0.05$).

Meta-analysis

Integration of the results of this case-control study with the Meta-analysis done previously yielded a pooled *OR* of 1.34 (95%*CI*: 1.19–1.50). The results were consistent with previous studies (Fig. 1).

Sensitivity analysis

A subgroup analysis was conducted to evaluate the association between HBV infection and the risk of GC across different sex and age groups (Fig. 2). The results showed that HBV infection was associated with an increased risk of GC in most subgroups of the population ($P < 0.05$). Meanwhile, no multiplicative interaction was found between sex, age and HBV. To evaluate the potential impact of unmeasured confounding on the association between HBV infection and GC, we conducted an E-value sensitivity analysis (Table 6). The analysis indicates that unmeasured confounders would need to exert a 2.402-3.069-fold effect to nullify the main findings (i.e., reduce the estimated risk ratio to 1.0), regardless of whether the variables were adjusted for. This suggests that our results are robust against unmeasured confounding.

Discussion

Our present case-control study provided evidence in support of the association between HBsAg seropositivity and increased risk of GC. We also observed a possible additive interaction between HBV infection and smoking on GC. Furthermore, the results of our case-control study were mostly consistent with our Meta-analysis.

In our country, there is a very high prevalence of hepatitis B virus as well as Helicobacter pylori. At the meantime, these are high risk factors for various types of cancer [24, 25]. In the past, HBV was often thought to be closely associated with the development of cirrhosis and liver tumors [26]. However, recent findings have shown that HBV is also associated with the development of many extrahepatic tumors, including endometrial, cervical, colorectal and gastric cancers [27, 28]. A Mendelian

Table 2 Univariate and multivariate logistic regression analysis of HBV infection and gastric cancer

Research factor	Case	Control	Univariate	Model1	Model2	Model3
	n(%)	*n*(%)	OR(95%CI)	OR(95%CI)	OR(95%CI)	OR(95%CI)
HBV						
No	355(86.80)	1196(93.80)	1	1	1	1
Yes	54(13.20)	79(6.20)	2.30(1.60,3.32)	3.53(2.05,6.06)	3.36(1.91,5.91)	3.30(1.84,5.91)

Note: Model 1 adjusted for sex, age; Model 2 adjusts for sex, age, marital status, education level, income; Model 3 adjusted for sex, age, marital status, education level, income, BMI, smoke, drink, drinking tea, taste, history of diabetes, history of hypertension

Table 3 Multiplicative interaction analysis of HBV infection and smoking with GC

Research factor		Case *n*(%)	Control *n*(%)	Multiplicative interaction OR(95%CI)
HBV	Smoke			
No	No	177(43.28)	852(66.82)	1
No	Yes	178(43.52)	344(26.98)	2.00(1.19,3.34)
Yes	No	33(8.07)	51(4.00)	4.27(1.97,9.26)
Yes	Yes	21(5.13)	28(2.20)	4.73(1.85,12.08)
HBV*Smoke				0.55(0.17,1.79)

Note: Adjusted for sex, age, marital status, education level, income, BMI, smoke, drink, drinking tea, taste, history of diabetes, history of hypertension

Table 4 Indicators for evaluating the additive interaction between HBV infection and smoking and alcohol consumption on gastric cancer

Research factor	RERI[a](95%CI)	API[b](95%CI)	S[c](95%CI)
HBV*Smoke	18.95(-2.41,40.32)	0.78(0.67,0.90)	5.45(3.26,9.08)
HBV*Drink	0.36(-1.56,2.28)	0.11(-0.43,0.66)	1.20(0.48,2.99)

Note: Adjusted for sex, age, marital status, education level, income, BMI, smoke, drink, drinking tea, taste, history of diabetes, history of hypertension; a: relative excess risk of interaction (RERI); b: attributable proportion of interaction (API); c: the synergy index (S)

Table 5 Multiplicative interaction analysis of HBV infection and drink with GC

Research factor		Case *n*(%)	Control *n*(%)	Multiplicative interaction OR(95%CI)
HBV	Drink			
No	No	258(63.08)	684(53.65)	1
No	Yes	97(23.71)	512(40.16)	0.32(0.20,0.50)
Yes	No	39(9.54)	40(3.14)	3.51(1.62,7.59)
Yes	Yes	15(3.67)	39(3.06)	0.96(0.39,2.34)
HBV*Drink				0.87(0.27,2.81)

Note: Adjusted for sex, age, marital status, education level, income, BMI, smoke, drink, drinking tea, taste, history of diabetes, history of hypertension

randomization study examined the causal relationship between HBV infection and extrahepatic cancers, and the results supported the existence of a causal relationship between the two, mainly with cervical (*OR*: 1.57, 95%*CI*: 1.29–1.91) and gastric (*OR*: 1.12, 95%*CI*: 1.05–1.19) cancers [27]. Currently, the results of association studies between HBV infection and GC are inconsistent. Previous Meta-analysis showed that the risk of GC was higher in HBV-infected than in HBV-uninfected individuals, with an *OR* range of 1.26–1.49 [29–31]. However, another study showed that HBV infection was associated with certain precancerous lesions, but not with GC [32]. Therefore, it is necessary to explore the potential link between HBV infection and GC in depth.

In this study, the association between HBV infection and the risk of GC in the Fujian population was explored in detail by collecting information on GC patients and patients undergoing health checkups in various hospitals in Fujian. The findings showed that the risk of GC in HBV-infected patients was 2.3 times higher than that in HBV-uninfected patients (95%*CI*: 1.60–3.32). After adjusting for confounders, the *OR* was significantly greater, and HBV infection increased the risk of developing GC. The conclusion is robust after integrating the results of the case-control study into the prior Meta-analysis.

Alcohol consumption by HBV-infected individuals has received much attention in recent years. Several studies have shown that alcohol can affect HBV transcriptional replication and amplify the damaging effects of HBV [33]. However, when the interaction was explored, no multiplicative or additive interaction between the two was found. However, in the HBV-uninfected population, the risk of GC was lower in alcohol drinkers than in non-alcohol drinkers. This may be related to the amount of alcohol consumed. Some studies found that light alcohol consumption may be associated with a lower risk of GC in women [34]. Moderate alcohol consumption may be protective against GC in women [34]. It is the heavy drinking that may increase the risk of GC [35]. In people who do not drink alcohol, HBV infection greatly increases the risk of GC in the population [36].

Meanwhile, this study also explored the interaction between HBV infection and smoking and an additive interaction was found. There is substantial evidence that extensive oxidative stress occurs in hepatitis B, which in turn induces cancer [37]. Smoking is also an independent risk factor for various types of gastrointestinal cancers [38]. In the present study additive interaction analysis, it was found that the risk of GC when HBV infection and smoking coexisted was 5.45 times higher than when they existed independently. This may be due to the fact that tobacco is an inducer and promoter in the process of GC triggered by HBV infection, which has the effect of reinforcing or promoting carcinogens. However, the

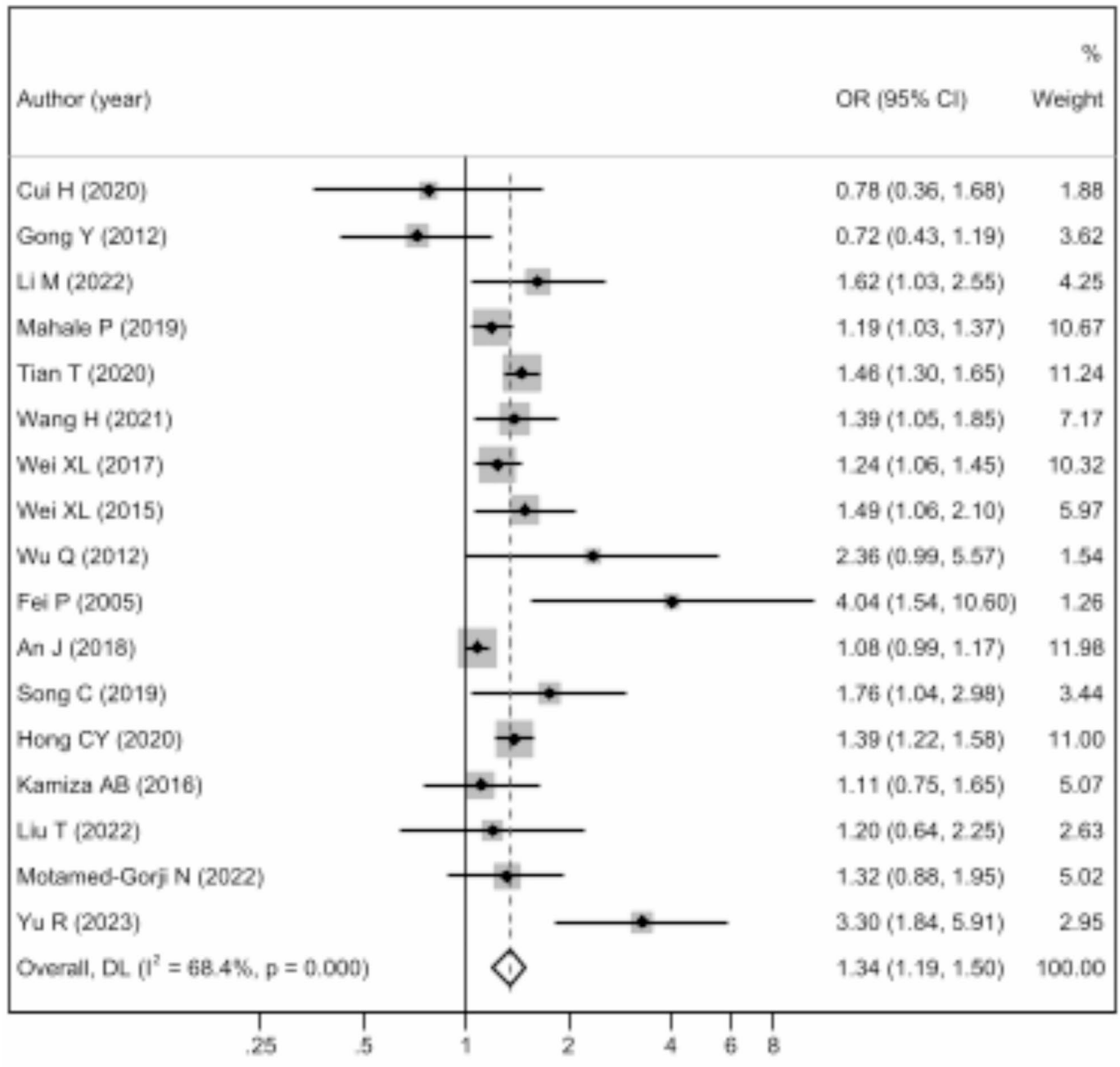

Fig. 1 Forest plot of association meta-analysis of HBV and GC risk

mechanism of cancer promotion needs to be further explored.

Most studies have explained the mechanism by which HBV induces hepatocellular liver cancer [39]. However, the mechanism of association between HBV and gastric carcinogenesis has not been fully elucidated. It may be related to a variety of potential mechanisms, including chronic inflammation, systemic immune impairment, and direct effects of HBV proteins on tumorigenesis and/or oncogenes [20, 40]. A previous study found that in patients with HBV-infected gastric or pancreatic cancer, the expression of HBV-encoded X (HBX) protein was higher in cancer cells [21]. In addition, chronic inflammation caused by HBV infection induces cellular heterogeneity and promotes cancerous transformation of gastric epithelial cells [23]. An impaired immune system also plays a crucial role in gastric carcinogenesis linked to HBV infection. Infection-related factors increase the risk of gastric cancer, which may occur through suppression of the immune system [41]. In addition to the above mechanisms, cirrhosis may also play an important role in the development of gastric cancer [42]. The exact mechanism of the association between HBV infection and the risk of GC still needs to be further investigated.

There are several limitations to our study. First, potential selection bias in case-control studies is difficult to

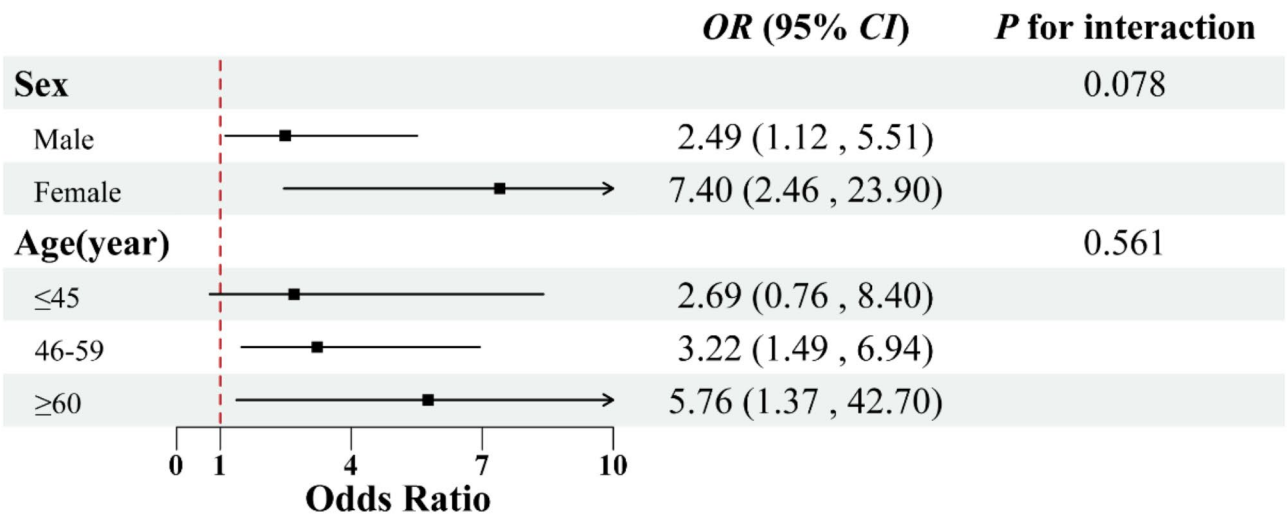

Fig. 2 Forest plot of subgroup analysis on the association between HBV and GC risk

Table 6 E values for the association between HBV infection and gastric cancer

Model	E-value for point estimate	Lower limit of 95%CI
Univariate	2.402	1.844
Model1	3.163	2.218
Model2	3.069	2.109
Model3	3.035	2.052

Note: Model 1 adjusted for sex, age; Model 2 adjusts for sex, age, marital status, education level, income; Model 3 adjusted for sex, age, marital status, education level, income, BMI, smoke, drink, drinking tea, taste, history of diabetes, history of hypertension

avoid when cases and controls are recruited exclusively from hospitals. Hospitalized patients often have characteristics different from those of the general population. These characteristics may be associated with HBV infection, which in turn leads to bias in the estimation of the association between HBV infection and gastric cancer. However, we further confirmed the robustness of our results through subgroup analyses and found no significant interactions between sex, age, and HBV. Second, in this case-control study, it was not possible to determine the casual and direct associations between HBV and GC. Third, we did not have information on other HBV markers, such as HBV-DNA, which prevented us from categorizing the population more accurately. Also, when collecting general lifestyle habits, specific information, such as the amount of alcohol consumed and the amount of cigarettes smoked, was not collected in detail, which prevented further and more in-depth exploration of the study variables. Helicobacter pylori is known to be a clear risk factor for GC, and this study failed to collect information on H. pylori infection in the study population. Thus, the effect of confounding interference of H. pylori in the study could not be ruled out. Lastly, our calculated E-values suggest that the observed association is unlikely to be fully explained by residual confounding, yet we cannot entirely rule out the potential influence of unmeasured or unknown factors, which underscores the need for cautious interpretation of our findings.

In conclusion, this study illustrates and proves the association between HBV infection and the risk of GC in a multifaceted way through a hospital-based case-control study and Meta-analysis. Meanwhile, the additive interaction between smoking and HBV infection on gastric cancer was revealed. The results of this study have an important practical value: for HBV-infected populations, we should not only screen for the development of liver disease, but also focus on the development of other extrahepatic tumors, especially gastric cancer.

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Author contributions
PXE designed the study. CDJ, YR, CYF, ZH, and JYJ collected the data. CDJ and YR analyzed the data. CDJ and YR contributed to the interpretation of results. CDJ and YR drafted the manuscript. PXE, WYL revised the manuscript. All authors have discussed the results and commented on the manuscript. All authors read and approved the final manuscript.

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Data availability
The datasets used can be available from the corresponding author on reason-able request.

Declarations

Ethics approval and consent to participate
The current study was carried out in compliance with the Declaration of Helsinki, and the Ethics Committee of Fujian Medical University approved the study protocol (ethics number 2024233). All subjects provided their informed consent prior to participating in this study.

Competing interests
The authors declare no competing interests.

Declaration of competing interest
The authors have no conflicts of interest to declare.

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