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Interaction between Cigarette Smoking and HBV or HCV Infection on the Risk of Liver Cancer: A Meta-Analysis

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Abstract

Introduction—Chronic infection with HBV and HCV as well as cigarette smoking are established risk factors of hepatocellular carcinoma (HCC), but it is unclear whether an interaction exists between these factors in causing hepatocellular carcinogenesis. We conducted a meta-analysis to evaluate the interaction of HBV and HCV infection and cigarette smoking on the risk of HCC.

Methods—We systematically searched the PUBMED and the China National Knowledge Infrastructure (CNKI) databases. A total of 16 eligible publications were identified. Cigarette smoking, and chronic HBV and HCV infections were dichotomized into present or absent. Additive (S) and multiplicative interaction indexes (V) between smoking and each of the two infections and their 95% confidence intervals (95% CI) were calculated for each study and then combined in a meta-analysis.

Results—We found a more than additive interaction between HBV infection and cigarette smoking (S=1.44, 95% CI=1.00–2.06; 9 studies) and a more than multiplicative interaction (V=1.60, 95% CI=1.16–2.20; 6 studies) between HCV infection and cigarette smoking. No publication bias was detected.

Conclusion—Smoking appears to interact with both HBV and HCV in determining HCC risk. A pooled analysis of individual subject data, with appropriate adjustment with other risk factors is warranted to confirm these results.

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Impact—Chronic carriers of HBV and HCV are suggested to avoid smoking.

Keywords

Cigarette smoking; HBV; HCV; HCC; interaction

Introduction

Liver cancer is the sixth most common cancer and the third most common cause of death from cancer worldwide with about 600,000 estimated new cancer cases and about the same number of deaths in 2002 (1). China alone accounts for about 55% of the world burden of liver cancer (1). The 5-year survival rates for liver cancer are low, at 12% in the United States during 1996–2004(2), 9% in Europe during 1995–1999 (3), and 5% in developing countries in 2002 (1). Hepatocellular carcinoma (HCC) represents the main histologic type of liver cancer. The main risk factors for HCC are chronic infection with hepatitis B and C viruses (HBV and HCV), alcohol drinking, tobacco smoking, and aflatoxin exposure. Oral contraceptive usage, iron overload, overweight and diabetes are also known or suspected risk factors of the disease (4)

The risk of HCC in people infected with HBV or HCV is about 20 times higher than in those who are not (5). HCC cases from Asia (except Japan), Africa, Latin America, and Greece are mainly attributed to HBV infection while those cases from other European countries, northern America and Japan are mainly attributed to HCV (6). Overall, the attributable fraction of HBV on HCC is 54.4%, with 23.3% in high-income countries and 58.8% in low- and middle-income countries (7). Thirty-one percent of HCC cases worldwide are attributed to HCV, with 19.9% in high income countries and 33.4% in low- and middle-income countries.

The International Agency for Research on Cancer (IARC) had classified HCC as one of the tobacco-related cancers in 2004 (8). A recent meta-analysis reported a moderate risk of HCC with current cigarette smoking status (meta-RR=1.51, 95% CI=1.37–1.67) (9). Residual confounding from HBV and HCV infection has long been an issue to establish whether cigarette smoking is a risk factor of HCC. Adjustment for and stratification by HBV or HCV status were considered to evaluate the effect of smoking on the risk of HCC (8, 9).

Though the independent effects of HBV and HCV infection, and of cigarette smoking on the risk of HCC have been established, the possible interaction between these factors is not well characterised. The data from individual studies on the interaction between HBV infection and smoking are not fully consistent. Some studies observed an association between cigarette smoking and HCC only among HBV negative (HBV−) persons (10–13), some studies reported associations in HBV carriers (HBV+) (14, 15), but other studies reported no interaction (16–18). Nevertheless, most studies observed an interaction between cigarette smoking and HCV infection on the risk of HCC (18–21). In consistencies among studies can be due to random fluctuations, because of small number of cases, or to systematic differences in study design.

To better elucidate the independent and combined effect of cigarette smoking and HBV and HCV infection in the etiology of HCC, we conducted a meta-analysis to evaluate the interactions between these factors in determining HCC risk.

Material and Methods

Search Strategy and Selection Criteria (Figure 1)

We systematic searched the PUBMED database with the following keywords: (HBV OR HCV) AND (Smoking [Mesh] OR Tobacco [Mesh]) AND (Liver cancer [Mesh] OR HCC [Mesh]) from 1966 to May 2009. The search was not restricted as to language. In view of the large number of HCC cases arising in China, we aimed at including also studies conducted in this country and reported in national scientific journal not indexed in PUBMED. Therefore, we also searched the China National Knowledge Infrastructure (CNKI) database, with the same keywords. The CNKI database includes papers published in Chinese journals after 1994. In addition to the databases, we checked the references list of the articles retrieved from PUBMED and CNKI.

Overall, 48 publications were identified in PUBMED and an additional 13 articles were identified from their reference lists. In 30 of these publications, results on either joint effect of HBV or HCV and smoking or effect of smoking stratified by HBV/HCV status were reported. We excluded publications in which the study population was restricted to HBV carriers (four publications) or non-carriers only (three publications). In addition, we excluded seven publications due to the following reasons: only stratified results were reported, which made it impossible to estimate the variance of the interaction indexes; inclusion in later reports of the same studies; and information on HBV and smoking collected at the baseline without exposure distribution at end point.

Of the 9 additional publications which were identified from the CNKI (including one meta-analysis of risk factors of HCC), none presented detailed information on the combined effect of HBV, HCV, and cigarette smoking. Thus, all identified publications from CNKI were excluded from this analysis.

In total, 16 publications were included in this current meta-analysis. Their characteristics are listed in Table 1. Nine studies provided results on the interaction between cigarette smoking and HBV infection and six studies were considered to estimate the interaction with HCV infection on the risk of HCC. Since the fatality of HCC is high, results based on mortality or incidence were combined. No studies provided results on the interaction between cigarette smoking and combined HBV and HCV infections.

Statistical Analysis

We categorized study subjects into four groups with respect to infection and smoking: Non-HBV/HCV infected and never-smokers (reference category), non-HBV/HCV infected and ever-smokers (RR_{01}), HBV/HCV infected and never-smokers (RR_{10}), and HBV/HCV infected and ever-smokers (RR_{11}). The number of subjects in each stratum and the adjusted risk estimates (if available) were recorded. If the latter were not available, crude relative risks were calculated from the numbers of subjects and person-years reported in the tables.

Additive (S) and multiplicative interaction indexes (V) between each infection and cigarette smoking status and their 95% confidence intervals (95% CI) were calculated for each study (22).

$$S=(RR_{11}-1)/(RR_{01}+RR_{10}-2)$$
$$\text{For cohort study, } Var(S)=F1+F2-4\times F3$$

Where $F1=(Var(R_{11})+Var(R_{00}))/(R_{11}-R_{00})^2$

$F2=(Var(R_{01})+Var(R_{10})+4Var(R_{00}))/(R_{01}+R_{10}-2R_{00})^2$

$F3=Var(R_{00})/((R_{11}-R_{00})(R_{01}+R_{10}-2R_{00}))$

$Var(R_{ij})=R_{ij}/M_{ij}$, where M_{ij} is the total number in the joint category

R_{ij} is the risk of the specific category, where i=1 refers to the exposure of HBV or HCV infection, i=0 refers to no virus exposure; j=1 refers to the exposure of the cigarette smoking, j=0 refers to no cigarette smoking exposure.

$$\text{For case-control study, } Var(S)=F4+F5-F6$$

Where $F4=Var(RR_{11})/(RR_{11}-1)^2$

$F5=Var(RR_{01})+(Var(RR_{10})+2cov(RR_{01}, RR_{10}))/(RR_{01}+RR_{10}-2)^2$

$F6=2cov(RR_{11}, RR_{01}+RR_{10})/((RR_{11}-1)(RR_{01}+RR_{10}-2))$

$Var(RR_{ij})=RR_{ij}^2\times(1/a_{ij}+1/c_{ij}+1/b+1/d)$

$Cov(RR_{01}, RR_{10})=RR_{01}\times RR_{10}\times(1/b+1/d)$

$Cov(RR_{11}, RR_{01}+RR_{10})=RR_{11}\times(RR_{01}+RR_{10})\times(1/b+1/d)$

Where “b” and “d” are the frequency of cases and controls, respectively, in the reference category and “a_{ij}” and “c_{ij}” are the frequency of cases and controls in the exposed category.

$$V=RR_{11}/(RR_{01}\times RR_{10}).$$
$$\text{For cohort study, } Var(V)=1/a+1/b+1/e+1/f$$
$$\text{For case-control study, } Var(V)=1/a+1/b+1/c+1/d+1/e+1/f+1/g+1/h$$

Where “a” to “d” are the numbers of cases and controls classified with respect to HBV or HCV infection and “e” to “h” are the corresponding numbers with respect to smoking, and the two exposures are assumed to be independent.

Overall additive and multiplicative interaction indexes were then calculated using random-effects models to combine the study-specific interaction estimates.

In order to explore sources of heterogeneity, subgroup analysis were performed by study design (case-control and cohort studies), region (Asia and non-Asia), and vital status of

cases (incidence and mortality). Heterogeneity of the estimates across studies was tested, using a non-iterative weighted method (23). Egger's test was utilized to assess the presence of publication bias (24). Sensitivity analyses were performed by removing one study at a time to assess whether the meta-estimates were strongly influenced by any particular study.

To explore the effect of cigarette smoking, independent of both HBV and HCV infection, on the risk of HCC, we also abstracted results from publications on the HBV and HCV negative or HBV and HCV positive groups.

Results

Interaction between HBV infection and Cigarette Smoking

Among the nine studies selected for the HBV analysis, five were case-control studies, and the other four were cohort studies. Six of the studies were from Asia (China, Hong Kong, Japan, Korea, and Taiwan), two were from Greece, and the remaining study was from USA. Two of the studies used mortality data (Table 1).

Overall, relative to HBV-negative nonsmokers, the risk of HCC was 1.87 (95% CI=1.30–2.69) for HBV negative smokers, 15.8 (95% CI=9.69–25.7) for HBV positive non-smokers and 21.6 (95% CI=15.2–30.5) HBV positive smokers. These results suggested a more than additive interaction between these two risk factors (S=1.44, 95% CI=1.00–2.06), and were compatible with a multiplicative interaction (V=0.87, 95% CI=0.58–1.29) (Table 2). The results were similar after exclusion of a large cohort study from Korea, thought the test for the departure from the additive model of interaction included the null value (S=1.51, 95% CI=0.85–2.66 and V=0.78, 95% CI=0.47–1.29). No heterogeneity in the results of the meta-analysis were suggested by study design, region, and source of cases (supplement Table 1)

Interaction between HCV infection and Cigarette Smoking

Six studies provided data relevant to the evaluation of the joint effect of HCV infection and cigarette smoking on the risk of HCC (Table 3). Four of them were case-control studies and two were cohort studies. The relative risk of HCC was 1.50 (95% CI=1.25–1.80) for cigarette smokers among HCV negative subjects, 7.94 (95% CI=4.40–14.3) for HCV positive subjects among non-smokers, and 23.1 (95% CI=9.43–56.8) for the joint effect of cigarette smoking and HCV infection. The overall interaction terms were 3.32 (95% CI=2.23–4.94) based on additive model and 1.60 (95% CI=1.16–2.20) on the multiplicative model. The Egger's test suggested no publication bias in these studies (p=0.511 for S and 0.696 for V). No heterogeneity in the results of the meta-analysis was suggested by study design or by region (supplement Table 2)

Smoking effects among HBV and HCV negative subjects

The combined result based on the crude estimates from the two (25, 26) studies in which ever smoker was compared to never smoker among the HBV and HCV negative subjects was 2.47 (95% CI=1.41–4.32) and it was 0.80 (95% CI=0.15–4.30) based on the adjusted estimates from another set of publications (25, 27) (Table 4). The negative result of the meta-analysis of the adjusted RR is due to a single study (27).

Smoking effects among HBV and HCV positive subjects

There were few publications on the three-way interaction among HBV, HCV, and smoking. This was probably due to the difficulty of identifying an appropriate control group with co-infection by HBV and HCV. In a cohort study in southern Taiwan (27), no association was reported between smoking and HCC (RR=1.1, 95% CI=0.3–4.4,) in the coinfected population (n=134, 2% of the cohort, 12 HCC cases) after 8 years of follow-up.

Discussion

The results from our study suggest an interaction on the additive scale between cigarette smoking and HBV infection and an interaction on the multiplicative scale with HCV infection. In addition, our results support the notion that cigarette smoking has a measurable effect on HCC risk even in the absence of HBV or HCV infection.

Several theories have been proposed for the role of cigarette smoking in liver carcinogenesis and its potential interaction with viral infection. Cigarette smoke contains several chemicals which are metabolized and activated as carcinogens in the liver (28), and it can therefore act as an initiator in the liver carcinogenesis, while HBV and HCV mainly act as a promoter through chronic inflammation and cell 13 proliferation through chronic hepatitis and liver cirrhosis (5). In addition, cigarette smoking may contribute to progression from chronic HBV and HCV infection to HCC (15, 29, 30). An action on different stages of carcinogenesis would be compatible with a multiplicative interaction index close or equal to 1, as in the case of HBV infection and cigarette smoking. A multiplicative interaction index >1, as in the case of HCV infection and cigarette smoking, if real, would imply a biological interaction between the two factors.

A cohort study conducted in southern Taiwan showed that cigarette smokers had higher prevalence of HCV infection, but such an association was not observed with HBV prevalence (31). In addition, smoking tended to be associated with elevated alanine aminotransferase levels only among HCV infected individuals (32) Cigarette smoking may worsen the prognosis of chronic HCV infection, possibly through the accumulation of oxidative stress (33, 34, 34), impaired immune response (35), and generation of insulin resistance (36, 37), which are also associated with HCV-related HCC (38).

An alternative explanation could be uncontrolled confounding, particularly by alcohol drinking. In one study, the interaction of alcohol drinking with HCV on HCC risk was observed to be stronger than that with HBV (39). As smoking and drinking are correlated in many populations, it is difficult to rule out a potential confounding effect by alcohol drinking.

The difference between the crude and adjusted estimates of cigarette smoking on the risk of HCC among the HBV and HCV negative population is difficult to interpret because the two estimates were based on different publications and should be interpreted with caution. Only one study contributed to both estimates (25) and there was only a small change in the risk estimate after adjusting for age, sex, race, education, alcohol, and diabetes (1.88 vs. 1.70). The two studies, which showed conflicting results, were both from Taiwan. In the Seven-

Township study (26), no effect was shown for former smokers (RR=1.00, 95% CI=0.22–4.59, compared to never smokers) but there was an increased association for current smokers after adjustment for age and sex (RR=2.44, 95% CI=1.17–5.00). In the A-Lein study (27), smoking habit was not associated with HCC risk (RR=0.3, 95% CI=0.1–1.4) after adjusting for age, sex, alcohol consumption, body mass index, and diabetes status. Whether the difference in results was due to the definition of smoking, change of smoking habit during follow-up, the characteristics of the study populations, or by chance needs further investigations.

One limitation of our meta-analysis was the fact that the authors of some studies did not provide adjusted risk estimates and only crude risk estimates was calculated based on the raw numbers reported in the original publications, leaving open to the possibility residual confounding in particular by age, sex, and alcohol drinking. A pooled analysis of individual data is warranted to overcome such a limitation.

Another limitation was the fact that methods used to measure HBV and HCV infection were different across studies. HBsAg positive for six months are generally considered as HBV carrier (40). Negativity for HBsAg combined with positivity for anti-HBs or anti-HBc indicates vaccination or ability to clear the infection (41). HBeAg is usually related to virus replication and infectivity (41). In all studies included in the present meta-analysis, test for HBsAg was one of the criteria for HBV infection; but in some studies, tests for anti-HBc (14, 18) and HBeAg (42) were also used. However, sensitivity analysis by excluding these studies did not reveal differences in the overall results.

Anti-HCV is the most common marker used to test for HCV infection. Two studies in the analysis used second-generation ELISA (16, 21), one study used the third-generation (18), and the others did not specify the assays used to measure anti-HCV. As the technique improves, the third-generation ELISA can identify 97% HCV infection but might be less specific than the second-generation ELISA (43). However, the results did not differ by excluding the study using third generation ELISA.

In conclusion, our meta-analysis found an interaction between cigarette smoking and both HBV and HCV infection, respectively. The pattern of the interaction seems different between the two infections, which might reflect their different roles in liver carcinogenesis. In addition, the carcinogenic effect of cigarette smoking on HCC risk appeared to be independent from infection with either HBV or HCV.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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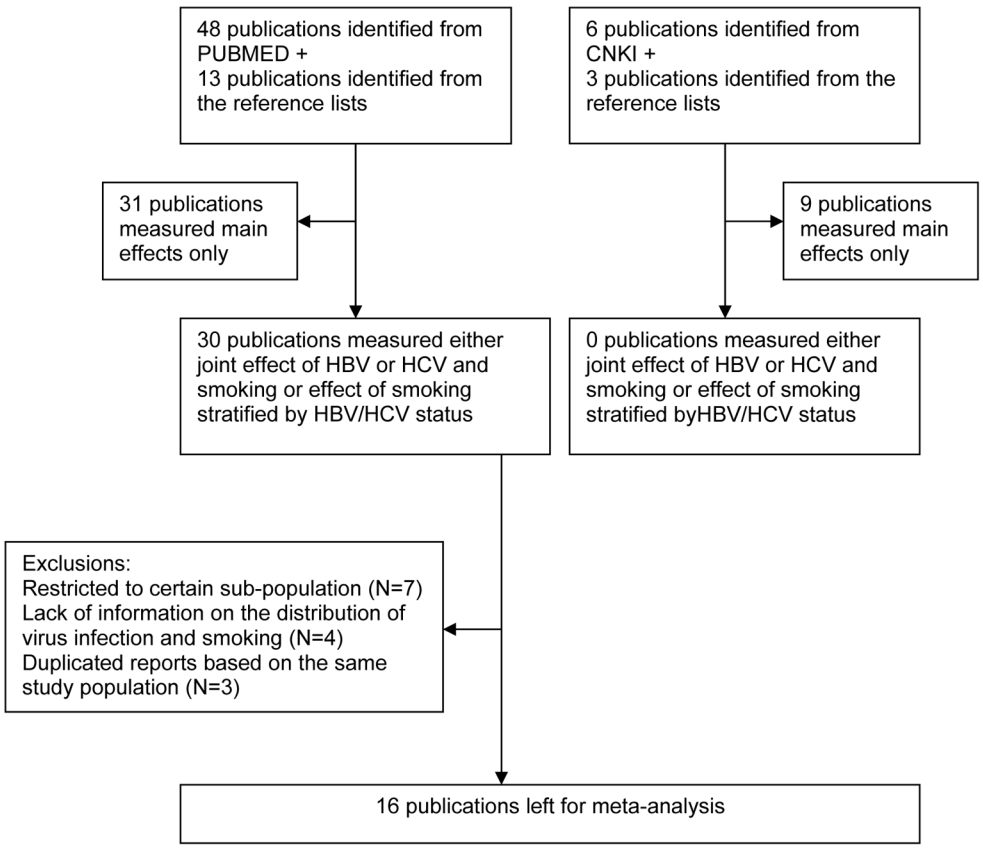

Figure 1.
Flow-chart of selection of publications included in the meta-analysis

Table 1

Summary characteristics of the studies selected

Author, year	Study Period	Country	Age	Study Design	Case	Number of case	HBV/HCV markers	Smoking definition
For HBV analysis								
Hassan, 2008 (18)	2000–2006	US	All ages	Case-control	Incident	319	HBsAg, anti-HBc	≥100 cigarettes lifetime
Jee, 2004 (17)	1993–2002	Korea	30–95	Cohort	Mortality	3807	HBsAg	Ever smoker
Wang, 2003 (10)	1991–2000	Taiwan	30–65	Cohort	Incident	115	HBsAg	4 days per week for a year
Mori, 2000 (16)	1992–1997	Japan	30+	Cohort	Incident	22	HBsAg	≥100 cigarettes lifetime
Goritsas, 1995 (44)	1989–1992	Greece	All ages	Case-control	Incident/Prevalent	51	HBsAg	Ever smoker
Tzonou, 1991 (45)	1976–1984	Greece	All ages	Case-control	Incident/Prevalent	185	HBsAg	Smoker or stopped smoking for less than 3 years
Chen, 1991 (42)	1985–1987	Taiwan	All ages	Case-control	Incident	200	HBsAg, HBeAg	Ever smoker
Tu, 1985 (14)	1980–1982	China	40+	Cohort	Mortality	70	HBsAg, anti-HBc	Ever smoker
Lam, 1982 (12)	1977–1980	Hong Kong	All ages	Case-control	Incident/Prevalent	107	HBsAg	Ever smoker
For HCV analysis								
Hassan, 2008 (18)	2000–2006	US	All ages	Case-control	Incident	319	Third generation anti-HCV	≥100 cigarettes lifetime
Fujita, 2006 (20)	1988–1999	Japan	40–79	Nested case-control	Mortality	94	Anti-HCV	Ever smoker
Sun, 2003 (21)	1991–2001	Taiwan	30–65	Cohort	Incident	112	Second generation anti-HCV	4 days per week for a year
Mori, 2000 (16)	1992–1997	Japan	30+	Cohort	Incident	22	Second generation anti-HCV	≥100 cigarettes lifetime
Yu, 1991 (19)	1986–1987	Taiwan	All ages	Case-control	Incident	127	Anti-HCV	Ever smoker
Tzonou, 1991 (45)	1976–1984	Greece	All ages	Case-control	Incident/Prevalent	185	Anti-HCV	Ever smoker
HBV or HCV not specified								
Franceschi, 2006 (46)	1999–2002	Italy	41–84	Case-control	Incident	229	HBsAg, anti-HCV	1 cigarette per day for a year
Yuan, 2004 (25)	1984–2001	US	18–74	Case-control	Incident	295	HBsAg, anti-HBc, anti-HCV	Smoker or stopped smoking for less than 10 years
HBV− and HCV−								
Wang, 2009 (27)	1996–2004	Taiwan	35+	Cohort	Incident	111	HBsAg, anti-HCV	Smoker or stopped smoking for less than 6 months
Chen, 2008 (26)	1991–2004	Taiwan	30–65	Cohort	Incident	291	HBsAg, HBeAg, anti-HCV	4 days per week for a year
Yuan, 2004 (25)	1984–2001	US	18–74	Case-control	Incident	295	HBsAg, anti-HBc, anti-HCV	Smoker or stopped smoking for less than 10 years

Table 2

Risk estimates and 95% confidence intervals for the joint effects and interaction indexes between HBV and smoking

					Interaction Index	
	HBV−/Tob−	**HBV−/Tob+**	**HBV+/Tob−***	**HBV+/Tob+**	**Additive**	**Multiplicative**
All studies (N=9)						
No. of cases	272	960	419	1680	3331	3309
Random effect	1.00	1.87 (1.30–2.69)	15.8 (9.69–25.7)	21.6 (15.2–30.5)	1.44 (1.00–2.06)	0.87 (0.58–1.29)
Adjusted random effects*	1.00	1.59 (0.94–2.70)	18.27 (14.5–23.0)	21.7 (11.8–40.0)	1.53 (1.34–1.75)	0.77 (0.36–1.67)
p for heterogeneity		0.001	0.011	0.050	0.049	<0.001
Egger's test for publication bias					0.609	0.105

One cohort study in Asia reported 0 cases in the HBV+/Tob− category. Multiplicative interaction was not able to be calculated for this study.

Abbreviation: HBV−/Tob−: Reference category, non-HBV infection and non-smoker; HBV−/Tob+: Non-HBV infection and smoker; HBV+/Tob−: HBV infection and non-smoker; HBV+/Tob+: HBV infection and smoker

*Three publications provided adjusted estimates (10, 17, 18). The estimate was based on male population. All three publications adjusted for age. Other adjustments included race (18), education, residence, anti-HCV, (10, 18), marital status (18), alcohol, diabetes (17, 18), family history of HCC (10), family history of cancer (18), and liver function (10)

Table 3

Risk estimates and 95% confidence intervals for the joint effects and interaction indexes between HCV and smoking

					Interaction Index	
	HCV−/Tob−	**HCV−/Tob+**	**HCV+/Tob−**	**HCV+/Tob+**	**Additive**	**Multiplicative**
All studies (N=6)						
No. of cases	197	373	62	200	832	832
Random effect	1.00	1.50 (1.25–1.80)	7.94 (4.40–14.3)	23.1 (9.43–56.8)	3.32 (2.23–4.94)	1.60 (1.16–2.20)
Adjusted random effects*	1.00	1.42 (1.05–1.96)	6.90 (1.12–42.7)	19.6 (1.55–247.0)	3.36 (1.09–10.4)	1.83 (1.00–3.34)
p for heterogeneity		0.471	0.064	<0.001	0.755	0.697
Egger's test for publication bias					0.511	0.696

Abbreviation: HCV−/Tob−: Reference category, non-HCV infection and non-smoker; HCV−/Tob+: Non-HCV infection and smoker; HCV+/Tob−: HCV infection and non-smoker; HCV+/Tob+: HCV infection and smoker

*Three publications provided adjusted estimates (18, 19, 21). One of the publication was based on male (21), one is stratified by gender (18), and the other one adjusted for sex (19). All three publications adjusted for age. Other adjustments included race, residence (18, 19), marital status (18), education, HBV (18, 21) alcohol, diabetes, family history of cancer (18), and family history of HCC (21).

Table 4

Crude and adjusted risk estimates and 95% confidence intervals for smoking among HBV and HCV negative populations

Study	Crude OR/RR	95% CI	Adjusted OR/RR	95% CI
Wang, 2009 (27)			0.3	(0.1–1.4)
Chen, 2008 (26)	3.33	(1.93–5.76)		
Yuan, 2004 (25)	1.88	(1.15–3.07)	1.7	(1.0–3.0)
Pooled	1.86	(0.98–3.56)	0.98	(0.45–2.12)
P for heterogeneity	0.017		0.049	

Wang, 2009 (27) adjusted for age, sex, drinking, BMI and diabetes before the study.

Yuan, 2004 (25) adjusted for age, sex, race, education, drinking, and diabetes.