

Interaction between Cigarette Smoking and Hepatitis B and C Virus Infection on the Risk of Liver Cancer: A Meta-analysis

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Abstract

Introduction: Chronic infection with hepatitis B (HBV) and C viruses (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 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; nine studies) and a more than multiplicative interaction (V = 1.60; 95% CI, 1.16-2.20; six studies) between HCV infection and cigarette smoking. No publication bias was detected.

Conclusion: Smoking seems 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.

Impact: The results of this study imply the evidence of a synergistic effect between smoking and HBV or HCV infection on the risk of HCC. Thus, chronic carriers of HBV or HCV are recommended to avoid smoking. *Cancer Epidemiol Biomarkers Prev*; 19(5); 1261–8. ©2010 AACR.

Introduction

Liver cancer is the sixth most common cancer and the third most common cause of death from cancer worldwide with ~600,000 estimated new cancer cases and about the same number of deaths in 2002 (1). China alone accounts for ~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 to 2004 (2), 9% in Europe during 1995 to 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 ~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, whereas 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 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-relative risk, 1.51; 95% confidence interval (95% CI), 1.37-1.67; ref. 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).

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Although 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 characterized. 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 persons (10 11 12 13), some studies reported associations in HBV carriers (14, 15), but other studies reported no interaction (16 17 18). Nevertheless, most studies observed an interaction between cigarette smoking and HCV infection on the risk of HCC (18 19 20 21). Inconsistencies among studies can be due to random fluctuations, because of small number of cases, or to systematic differences in the 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.

Materials and Methods

Search strategy and selection criteria. We systematically searched the PUBMED database with the follow-

ing 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 also including studies conducted in this country and reported in national scientific journals not indexed in PUBMED. Therefore, we also searched the China National Knowledge Infrastructure (CNKI) database, with the same keywords. The CNKI database includes articles published in Chinese journals after 1994. In addition to the databases, we checked the references list of the articles retrieved from PUBMED and CNKI (Fig. 1).

Overall, 48 publications were identified in PUBMED and an additional 13 articles were identified from their reference lists. In 30 of these publications, the results on either the joint effect of HBV or HCV and smoking, or the 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

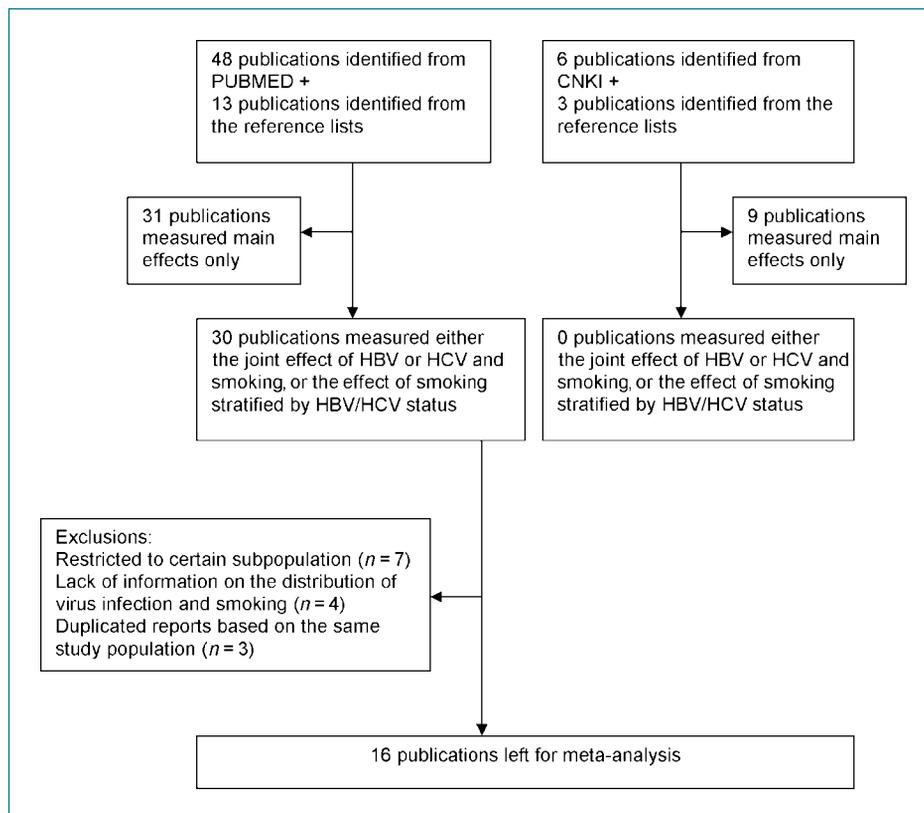


Figure 1. Flowchart of selection of publications included in the meta-analysis.

on HBV and smoking collected at the baseline without exposure distribution at end point.

Of the nine additional publications that 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. Because 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 (RR) 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% CIs were calculated for each study (22).

$$S = (RR_{11} - 1)/(RR_{01} + RR_{10} - 2)$$

For the cohort study, $\text{Var}(S) = F1 + F2 - 4 \times F3$

in which $F1 = (\text{Var}(R_{11}) + \text{Var}(R_{00}))/((R_{11} - R_{00})^2$

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

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

$\text{Var}(R_{ij}) = R_{ij}/M_{ij}$, in which M_{ij} is the total number in the joint category.

R_{ij} is the risk of the specific category, in which $i = 1$ 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, and $j = 0$ refers to no cigarette smoking exposure.

For the case-control study, $\text{Var}(S) = F4 + F5 - F6$ in which $F4 = \text{Var}(RR_{11})/(RR_{11} - 1)^2$

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

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

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

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

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

in which “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.

$$V = RR_{11}/(RR_{01} \times RR_{10}).$$

For the cohort study, $\text{Var}(V) = 1/a + 1/b + 1/e + 1/f$.

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

In which “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 effect models to combine the study-specific interaction estimates.

To explore sources of heterogeneity, subgroup analysis were done 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 noniterative weighted method (23). Egger's test was used to assess the presence of publication bias (24). Sensitivity analyses were done 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

Table 1. Summary characteristics of the studies selected

Author, year	Study Period	Country	Age, y	Study design	Case	No. of case	HBV/HCV markers	Smoking definition
For HBV analysis								
Hassan, 2008 (18)	2000-2006	U.S.	All ages	Case-control	Incident	319	HBsAg, anti-HBc	≥100 cigarettes lifetime
Jee, 2004 (17)	1993-2002	Korea	30-95	Cohort	Mortality	3,807	HBsAg	Ever-smoker
Wang, 2003 (10)	1991-2000	Taiwan	30-65	Cohort	Incident	115	HBsAg	4 d/wk 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 <3 y
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	U.S.	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 d/wk 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	U.S.	18-74	Case-control	Incident	295	HBsAg, anti-HBc, anti-HCV	Smoker or stopped smoking for <10 y
HBV- and HCV-								
Wang, 2009 (27)	1996-2004	Taiwan	35+	Cohort	Incident	111	HBsAg, anti-HCV	Smoker or stopped smoking for <6 mo
Chen, 2008 (26)	1991-2004	Taiwan	30-65	Cohort	Incident	291	HBsAg, HBeAg, anti-HCV	4d/wk for a year
Yuan, 2004 (25)	1984-2001	U.S.	18-74	Case-control	Incident	295	HBsAg, anti-HBc, anti-HCV	Smoker or stopped smoking for <10 y

were from Greece, and the remaining study was from U.S. 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 nonsmokers, 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 the exclusion of a large cohort study from Korea, although 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 (Supplementary Table S1).

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 RR 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 nonsmokers, 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 the 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 (Supplementary Table S2).

Smoking effects among HBV and HCV negative subjects. The combined result based on the crude estimates from the two (25, 26) studies in whichever smoker was compared with 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 (Table 4; refs. 25, 27). 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 coinfection 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 coinfecting 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

Table 2. Risk estimates and 95% CIs for the joint effects and interaction indexes between HBV and smoking

	HBV-/Tob-	HBV-/Tob+	HBV+/Tob-*	HBV+/Tob+	Interaction index	
					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)
$P_{\text{heterogeneity}}$		0.001	0.011	0.050	0.049	<0.001
Egger's test for publication bias					0.609	0.105

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

Abbreviations: HBV-/Tob-, reference category, non-HBV infection and nonsmoker; HBV-/Tob+, non-HBV infection and smoker; HBV+/Tob-, HBV infection and nonsmoker; HBV+/Tob+, HBV infection and smoker.

*Three publications provided adjusted estimates (Wang et al., 2003, Jee et al., 2004, and Hassan et al., 2008). The estimate was based on male population. All three publications adjusted for age. Other adjustments included race (Hassan et al., 2008), education, residence, anti-HCV, (Wang et al., 2003 and Hassan et al., 2008), marital status (Hassan et al., 2008), alcohol, diabetes (Jee et al., 2004 and Hassan et al., 2008), family history of HCC (Wang et al., 2003), family history of cancer (Hassan et al., 2008), and liver function (Wang et al., 2003).

Table 3. Risk estimates and 95% CIs for the joint effects and interaction indexes between HCV and smoking

	HCV-/Tob-	HCV-/Tob+	HCV+/Tob-	HCV+/Tob+	Interaction index	
					Additive	Multiplicative
All studies (<i>n</i> = 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)
<i>P</i> _{heterogeneity}		0.471	0.064	<0.001	0.755	0.697
Egger's test for publication bias					0.511	0.696

*Three publications provided adjusted estimates (Hassan et al., 2008, Yu et al., 1991, and Sun, et al., 2003). One of the publication was based on male (Sun, et al., 2003), one is stratified by gender (Hassan et al., 2008), and the other one adjusted for sex (Yu et al., 1991). All three publications adjusted for age. Other adjustments included race, residence (Hassan et al., 2008, and Yu et al., 1991), marital status (Hassan et al., 2008), education, HBV (Hassan et al., 2008 and Sun, et al., 2003), alcohol, diabetes, family history of cancer (Hassan et al., 2008), and family history of HCC (Sun, et al., 2003).

interaction with viral infection. Cigarette smoke contains several chemicals that are metabolized and activated as carcinogens in the liver (28) and it can therefore act as an initiator in the liver carcinogenesis, whereas HBV and HCV mainly act as a promoter through chronic inflammation and cell proliferation through chronic hepatitis and liver cirrhosis (5). In addition, cigarette smoking may contribute to the 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), 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 versus 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 with 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

Table 4. Crude and adjusted risk estimates and 95% CIs 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)
<i>P</i> _{heterogeneity}	0.017	0.049

NOTE: Wang, 2009 (27) adjusted for age, sex, drinking, body mass index, and diabetes before the study. Yuan, 2004 (25) adjusted for age, sex, race, education, drinking, and diabetes.

Abbreviation: OR, odds ratio.

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 it open to the possibility of 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. Subjects that are HBsAg positive for 6 months are generally considered as HBV carrier (40). Negativity for HBsAg combined with positivity for anti-HBs or anti-HBc indicates vaccination or the 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 seemed to be independent from infection with either HBV or HCV.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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