Interaction between Tobacco Smoking and Hepatitis B Virus Infection on the Risk of Liver Cancer in a Chinese Population

Xing Liu[1,2], **Aileen Baecker**[1], **Ming Wu**[3], **Jin-Yi Zhou**[3], **Jie Yang**[3], **Ren-Qiang Han**[3], **Pei-Hua Wang**[3], **Zi-Yi Jin**[2], **Ai-Min Liu**[4], **Xiaoping Gu**[4], **Xiao-Feng Zhang**[5], **Xu-Shan Wang**[5], **Ming Su**[6], **Xu Hu**[6], **Zheng Sun**[7], **Gang Li**[7], **Lina Mu**[8], **Na He**[2], **Liming Li**[9], **Jin-Kou Zhao**[3,*], and **Zuo-Feng Zhang**[1,*]

[1]Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles, CA

[2]Department of Epidemiology, School of Public Health, Fudan University, Shanghai, China

[3]Jiangsu Provincial Center for Disease Control and Prevention, Nanjing, Jiangsu, China

[4]Dafeng Center for Disease Control and Prevention, Dafeng, Jiangsu, China

[5]Ganyu Center for Disease Control and Prevention, Ganyu, Jiangsu, China

[6]Chuzhou County Center for Disease Control and Prevention, Chuzhou, Jiangsu, China

[7]Tongshan County Center for Disease control and Prevention, Tongshan, Jiangsu, China

[8]Department of Social and Preventive Medicine, School of Public Health and Health Professions, University at Buffalo, The State University of New York, Buffalo, NY

[9]Department of Epidemiology, School of Public Health, Peking University, Beijing, China

Abstract

Although tobacco smoking has been reported as a risk factor for liver cancer, few studies have specifically explored the association among Chinese females and the potential interaction between smoking and other risk factors. A population-based case-control study was conducted and 2,011 liver cancer cases and 7,933 healthy controls were enrolled in Jiangsu, China from 2003 to 2010. Epidemiological data were collected, and serum HBsAg and anti-HCV antibody were measured. Unconditional logistic regression was used to examine association and potential interaction, while semi-Bayes method was employed to make estimates more conservative. The prevalence of serum HBsAg positivity was 43.2% among cases and 6.5% among controls. The adjusted odds ratio for ever smoking was 1.62 (95% CI: 1.33 – 1.96) among male and was 0.82 (95% CI: 0.53–1.26) among female. Age at first cigarette, duration of smoking and pack-years of smoking were all significantly associated with liver cancer among men. Compared to HBsAg negative never-smokers, the adjusted OR was 1.25 (95% CI: 1.03–1.52) for HBsAg-negative ever smokers, was

Corresponding Author: Zuo-Feng Zhang, M.D., Ph.D., Professor of Epidemiology and Medicine, Associate Dean for Research, Fielding School of Public Health, University of California, Los Angeles, 71-225 CHS, Box 951772, Los Angeles, CA 90095-1772, U.S.A., Tel. 310-825-8418; Fax 310-206-6039, zfzhang@ucla.edu.
*Co-Senior Authors

7.66 (95% CI: 6.05–9.71) for HBsAg-positive never smokers, and was 15.68 (95% CI: 12.06–20.39) for HBsAg-positive ever smokers. These different odds indicated super-additive (RERI: 7.77, 95% CI: 3.81–11.73) and super-multiplicative interactions (ROR: 1.64, 95% CI: 1.17–2.30) between HBV infection and tobacco smoking. Most associations and interactions detected remained statistically significant after semi-Bayes adjustments. Tobacco smoking and HBV infection positively interact in the development of liver cancer.

Keywords

Liver cancer; Tobacco smoking; Population attributable risk; Interaction; Chinese population

Introduction

Tobacco smoke contains various carcinogens among which eleven were classified as IARC Group 1 human carcinogens.[1] It is causal for not only cancer of lung and upper aero-digestive tract which are exposed to tobacco smoke directly, but also for cancers of other organs including pancreas and lower urinary tract.[1] Epidemiologic evidence accumulated and a recent meta-analysis reported a positive association between current tobacco smoking and liver cancer risk (RR: 1.55, 95% CI: 1.46–1.65),[2] suggesting a causal role of smoking in liver cancer development.

The metabolites of several tobacco smoke carcinogens including benzo[a]pyrene (BaP), nicotine-derived nitrosamine ketone (NNK), N'-nitrosonornicotine (NNN) bind to DNA or cause genotoxicity.[1] The metabolism of these carcinogens relies on cytochrome P450 system.[3] On the other hand, cirrhosis due to excess alcohol consumption is an independent risk factor of liver cancer.[4] Alcohol as an inducer of the microsomal cytochrome P450 transformation system, may have impact on the activation and inactivation of carcinogenic chemicals including those from tobacco smoke.[5] It is possible that alcohol use may have an impact on metabolism of tobacco carcinogens in liver. Furthermore, chronic hepatitis B and C are major contributors to liver cancer, and account for more than eighty percent of liver cancer incidence.[6] Long-term inflammation, viral replication and irregular regeneration of the liver caused by hepatitis C, and oncogenic events including transactivation of proto-oncogenes, inactivation of tumor suppressor genes, impairment of DNA repair mechanisms, enhanced expression of growth factors and deregulation of cell cycle, etc. caused by the hepatitis B virus lead to cirrhosis and liver cancer development,[6] which will also affect the metabolic process of tobacco related carcinogens. Thus it is possible that chronic hepatitis, alcohol abuse and tobacco smoking may play a role in liver carcinogenesis both independently and jointly.

For individual epidemiologic studies, since liver cancer is a rare disease, some of the cohort and case-control studies were limited by sample size for more detailed exploration of the relative risk in subgroups of population, as well as for more comprehensive control of confounding due to hepatitis virus infection or excess alcohol consumption. Also, these methodological limitations make it difficult to evaluate potential interactions between smoking and other risk factors.[7,8] Most of the previously published studies used stratified

analyses to examine the potential heterogeneity in associations between tobacco and liver cancer. One meta-analysis reported a super-additive interaction between HBV infection and cigarette smoking (Synergy index = 1.44, 95% CI: 1.00–2.06), and a super-multiplicative interaction between HCV infection and cigarette smoking (Ratio of Odds Ratio = 1.60, 95% CI: 1.16–2.20) based on 9 and 6 studies, respectively.[9] However, these studies varied by study design and population, had different confounding variables controlled or reported crude ORs instead of adjusted ones, suggesting further investigation is needed.

No country in the world is more seriously affected by liver cancer than China, accounting for half of the world's incident liver cancer cases each year.[10] The prevalence of established risk factors such as hepatitis B virus infection, alcohol drinking and tobacco smoking are high in Chinese population. The prevalence of HBsAg positivity was estimated to be 7.2% in the general population aged 1~59 in 2006.[11] Meanwhile, it was reported that 52.9% men and 2.4% women were current smokers in 2010,[12] and 55.6% men and 15.0% women were current drinkers in 2007.[13] Most published studies have not explored the association between smoking and liver cancer among Chinese women due to inadequate sample size since Chinese women have a much lower prevalence of tobacco smoking. We conducted a population-based case-control study in Jiangsu Province with 2,011 newly diagnosed liver cancer cases and 7,933 healthy controls. The aim of this study was to evaluate the association between tobacco smoking and liver cancer among males and females and the interactions between tobacco smoking and other major liver cancer risk factors, including HBV infection, HCV infection, alcohol drinking and family history of liver cancer.

Methods

Study design

A population-based case-control study was conducted to explore risk factors of four common cancers, including lung, stomach, esophagus and liver cancer in Jiangsu Province, China from 2003 to 2010. A detailed description of the study design and data collection has been described elsewhere.[14] Four counties, including Dafeng, Ganyu, Chuzhou and Tongshan, in northern Jiangsu were selected as study sites, in which population-based cancer registries were established in the 1990s.

Subjects

Newly diagnosed liver cancer cases were enrolled from 1 January 2003 to 31 December 2010. Potential controls were identified from each county's demographic registry. Controls were required to be within the same gender and age group (±5 years) as cases. One healthy control was randomly selected from a list of eligible residents for each case. Both cases and controls were 18 years or older, had been residents at the study site for more than 5 years and had no history of cancer diagnosis. In this analysis, matching was broken and all controls from the four parallel studies were combined together to increase the statistical power. The participation rates were 37% for liver cancer cases and 87% for controls.

Data collection

The study was approved by the Institutional Review Board (IRB) of Jiangsu Provincial Health Department and the IRB of University of California, Los Angeles. Written informed consent was obtained from each participant before the in-person interview. Epidemiological data was collected during face-to-face interviews by trained public health professionals, using a standard questionnaire. Data on socio-demographic characteristics, tobacco use, alcohol drinking, diet and lifestyle, history of raw water drinking, exposure to mildew-contaminated food intake and family history of liver cancer were collected.

Tobacco smoking measurements were collected and defined in the following manner. Participants reporting a smoking history of 100 cigarettes or more were considered ever smokers; everyone else was considered never smokers. The ever smokers were then asked if they had ever quit smoking. If the participant answered yes, then the number of years since smoking cessation was collected. Those who quit smoking within one year were counted as current smokers. Ever smokers were asked about the types of tobacco they smoked, including cigarettes, water pipes and long-stemmed Chinese pipes. The age of first tobacco use, total years of smoking and number of cigarettes smoked every day were asked. If the participants smoked water pipes or long-stemmed Chinese pipes, the monthly amount of tobacco leaves consumed was recorded and then transformed to a corresponding number of cigarettes.

Six to eight mL of blood was collected from participants after the interview and processed and stored at the Jiangsu CDC in −70 °C freezers. Serum Hepatitis B virus surface antigen (HBsAg) and anti-HCV antibody were measured using enzyme-linked immunosorbent assay (ELISA) kits (Shanghai Kehua Diagnostic Medical Products Co., Ltd., China) according to the manufacturer's protocol.

Statistical analyses

All statistical analyses were performed using SAS 9.3 statistical software (SAS Institute Inc., Cary, NC). Student's t-test was used to compare the means of continuous variables between cases and controls. Chi-square tests were used to compare the distribution of categorical variables. Unconditional logistic regression was used to estimate the crude odds ratios (OR), adjusted ORs and their 95% confidence intervals (CI) in comparing liver cancer risk across levels of covariates. The confounding variables adjusted in the models included: study site (Dafeng, Ganyu, Chuzhou, Tongshan, entered into the models as dummy variables), gender (male, female), age (continuous), education level (illiteracy, primary school, middle school, high school and college, entered into the models as dummy variables), marital status (married, single, divorced or widowed), per capita family income 10 years ago (Yuan/year, RMB, continuous), body mass index (BMI, continuous), weekly alcohol intake in 1990s (mL/week, continuous), history of raw water drinking (yes or no), history of mildew-contaminated food intake (yes or no), HBV infection (HBsAg status, positive or negative), HCV infection (anti-HCV, positive or negative) and having family history of liver cancer (yes or no). Relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP), and synergy index (S) with 95% confidence intervals were calculated to examine interaction on the additive scale while ratio of the odds

ratios (ROR) was calculated to examine interaction on the multiplicative scale.[15] Let OR_{ij} be an approximation for the risk ratio in exposure category i,j, OR_{11}, OR_{10}, OR_{01}, OR_{00} be the odds ratios for each exposure categories, and $OR_{00} = 1$. $RERI = OR_{11} - OR_{10} - OR_{01} + 1$, $AP = RERI/OR_{11}$, and $S = [OR_{11} - 1]/[(OR_{10} - 1) + (OR_{01} - 1)]$.[15] To reduce the possibility of false positive findings after multiple comparisons performed in the analyses, a semi-Bayes (SB) approach was employed. The prior was set to have a coefficient of mean zero, corresponding to an OR of one (null, no association), with a variance of 0.5. This use of shrinkage estimation pulls the estimates toward the null, makes the posterior estimates more conservative and accurate than the observed ones.[16] A two-sided *P*-value less than 0.05 was considered statistically significant.

Results

Table 1 shows the socio-demographic characteristics of the 2,011 liver cancer cases and 7,933 controls included in this study. The mean age was 58.7 (SD = 12.2) years old for cases and 63.9 (SD = 11.4) years old for controls ($P < 0.001$). A higher proportion of cases was male, had at least an elementary education, and was married compared to controls ($P < 0.001$). Cases and controls also differed in per capita family income 10 years ago and in body mass index (BMI) ($P < 0.05$). For major risk factors of liver cancer, more cases were HBsAg positive (43.2% vs. 6.5%, $P < 0.001$), were ever drinkers (56.0% vs. 46.4%, $P < 0.001$) and had a family history of liver cancer (13.7% vs. 3.1%, $P < 0.001$). The prevalence of anti-HCV positivity was 0.9% among liver cancer cases and 0.8% among healthy controls ($P = 0.751$).

Among 7,933 controls, 57.9% of men and 17.4% of women were ever smokers, and 44.0% of men and 12.2% of women were current smokers. By comparison, 63.4% of men and 14.3% of women were ever smokers among the 2,011 cases, while 46.2% of men and 9.3% of women were current smokers. The association between tobacco smoking and the risk of liver cancer was analyzed altogether first and then by gender (Table 2). Overall, ever smoking was associated with liver cancer reporting an adjusted OR of 1.43 (95% CI: 1.20–1.70) after controlling for potential confounders and a posterior OR of 1.42 [95% posterior interval (PI): 1.20–1.69] after semi-Bayes adjustment. Current smokers had an adjusted OR of 1.43 (95% CI: 1.19–1.73) and a posterior OR of 1.42 (95% PI: 1.18–1.71) compared to never smokers, while former smokers showed adjusted OR of 1.88 (95% CI: 1.43–2.46) and posterior OR of 1.84 (95% PI: 1.41–2.40). Age of first tobacco use, daily amount of cigarettes smoked, duration of smoking in years and pack-years showed significant positive associations with liver cancer with evidence of a dose-response relationship ($P_{\text{for trend}} < 0.01$). The adjusted OR for ever smoking was 1.62 (95% CI: 1.33 – 1.96) among male and was 0.82 (95% CI: 0.53–1.26) among female. The associations between tobacco smoking and liver cancer were mainly observed among men, while no significant association was observed among women.

The potential interactions between tobacco smoking and other major risk factors of liver cancer were examined on both additive and multiplicative scales (Table 3). Compared to HBsAg negative never-smokers, the adjusted OR was 1.25 (95% CI: 1.03–1.52) for HBsAg-negative ever smokers, was 7.66 (95% CI: 6.05–9.71) for HBsAg-positive never smokers,

and was 15.68 (95% CI: 12.06–20.39) for HBsAg-positive ever smokers. The interaction was both super-additive, reporting RERI of 7.77 (95% CI: 3.81–11.73), AP of 0.50 (95% CI: 0.35–0.64) and S of 2.12 (95% CI: 1.53–2.94), and super-multiplicative, reporting ROR of 1.64 (95% CI: 1.17–2.30). The interaction between ever smoking and other major risk factors including anti-HCV positive was examined and no significant interaction was detected (Table 3).

Using the prevalence of ever smoking in the control group of 46.5% as the population prevalence, and using the adjusted OR of 1.43 as the approximation for the risk ratio, the population attributable risk of ever smoking was estimated to be 16.7%.

Discussion

In this large-scale population-based case-control study, tobacco smoking was confirmed to be positively associated with liver cancer with an adjusted OR of 1.43 (95% CI: 1.20–1.70) comparing ever smokers to never smokers after controlling for confounding and applying a conservative semi-Bayes adjustment. Stratified analyses by gender showed that the associations mainly existed in males. A positive interaction between smoking and HBV infection was detected.

We reported an adjusted OR of 1.43 (95% CI: 1. 19–1.73) for the association between current smoking and risk of liver cancer. This estimate was similar to the result from a meta-analysis for 38 cohort and 58 case-controls studies (mRR of 1.51, 95% CI: 1.37–1.67).[17] Former smoking showed higher ORs than current smoking with liver cancer in the analyses, probably because those who stopped smoking quitted due to weaker health conditions or onset of respiratory symptoms. Additionally, our estimate was based on a relatively comprehensive confounding control including adjustment for HBV infection, HCV infection, alcohol consumption, possibility of mildew contaminated food intake, raw water drinking and family history of liver cancer. Although we were not able to measure aflatoxin exposure directly, we asked about participants' historical intake of mildew contaminated food and included the variable in regression models. Furthermore, the semi-Bayes adjustment reported a similar estimate (SB-adjusted OR: 1.42, 95% PI: 1.20–1.69), confirming tobacco smoking as a moderate risk factor for liver cancer after accounting for major confounding.

Heterogeneity was found in the associations examined by gender. Positive associations between smoking behaviors and liver cancer were observed among men. Age at first tobacco use, daily amount of cigarette smoking, total years of smoking and pack-years of smoking were positively associated with liver cancer among male participants. Several cohort studies have been conducted among men[18–24] or have reported relative risks among men.[25,26] The Taiwan mortality study reported an age-adjusted RR of 1.46 (95% CI: 1.18–1.82) for current male smokers with a dose-response pattern.[26] Two other studies performed in Taiwan reported slightly increased but non-significant risks for smokers.[20,21] One study followed up 18,244 men in Shanghai and reported an RR of 1.8 (95% CI: 0.6–5.6) for ever smoking, adjusting for education level, HBsAg status, presence of urinary aflatoxins/DNA-adducts and heavy (30 g/day) alcohol consumption.[19,23] The Haimen study followed up 58,545

men and reported an age-adjusted RR of 0.9 (95% CI: 0.8–1.1) for current smokers.[25] The non-significant associations were probably due to the limited number of liver cancer cases that developed in the populations. Results for women in this study did not show significant association between cigarette smoking and liver cancer risk. Several cohort studies have reported increased risk for women who smoked compared to non-smokers,[25–27] while two cohorts from Korea and Japan did not observe a significant association.[28,29] None of these five studies controlled for viral hepatitis infection, and only one controlled for alcohol consumption. Based on these results and our observations, we have not found the conclusive evidence for association between tobacco smoking and liver cancer risk in female.

Positive interaction on both additive and multiplicative scale was detected between tobacco smoking and HBV infection. One meta-analysis examining the interaction between cigarette smoking and chronic HBV infection calculated S of 1.44 (95% CI: 1.00–2.06) and V (same as the ROR in our study) of 0.87 (95% CI: 0.58–1.29).[9] Our results provide further evidence with larger sample size and comprehensive confounding control. In previous studies, the associations between tobacco smoking and liver cancer stratified by HBV infection have been controversial. Some studies observed associations between heavy tobacco smoking and liver cancer risk among HBV positive participants,[30] while others observed significant associations only among HBV negative participants.[31–34] Our results suggest a joint effect between HBV infection and cigarette smoking in liver cancer development.

There were several limitations to this study. First of all, since liver cancer progresses very quickly, some cases deteriorated and were not able to participate in the study or died before being reached by our study staff. Selection bias may exist in our analyses because data was collected from those who tended to be in better health or were otherwise stronger than those who did not participate. Secondly, as a case-control study, all the exposure data was collected after disease diagnosis. Behaviors such as alcohol drinking and cigarette smoking among the cases might have changed after diagnosis and could inaccurately represent the lifetime exposure status, leading to an underestimation of the association. However, the interview was performed soon after the diagnosis, which may minimize the possibility of behavior change. Also, tobacco smoking was not a well-known risk factor for liver cancer in this population, and the likelihood of exaggeration in reporting this behavior would be low. Additionally, we used the history of possibility of mildew-contaminated food intake as a proxy of aflatoxin exposure in the regression models, which might suffer from residual confounding. The Shanghai men study reported RR of 2.4 (95% CI: 1.0–5.9) for aflatoxin metabolites of liver cancer,[19] which might indicate that our results may have underestimated the impact of aflatoxin exposure. Last but not least, our results showed that the association between tobacco smoking and liver cancer existed after adjusting for alcohol consumption, which was consistent with the observation from many other studies including those in Chinese populations.[23,35,36] However, since heavy smokers are more likely to be heavy drinkers as well, the possibility of over adjustment may exist when including alcohol consumption in the models.

In conclusion, we confirmed a positive association between tobacco smoking and risk of liver cancer in a Chinese population-based case-control study with a large sample size. This result is significant among males in this population. Positive interaction between tobacco

smoking and HBV has been observed. It is of importance to conduct tobacco interventions especially those targeting individuals with hepatitis B virus infection.

Acknowledgments

List of abbreviations

HBV	hepatitis B virus
HBsAg	hepatitis B surface antigen
OR	odds ratio
BMI	body mass index
ELISA	enzyme-linked immunosorbent assay
CI	confidence interval
RR	risk ratio
RERI	Relative excess risk due to interaction
AP	attributable proportion due to interaction
S	synergy index
SB	semi-Bayes

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Novelty and Impact

The study examined and confirmed the association between tobacco smoking and liver cancer risk in detail with a sufficient sample size from a population-based study in Chinese. Especially, the interaction between smoking and other risk factors was explored, and super-additive and super-multiplicative interactions were identified between smoking and HBV. Semi-Bayes correction was employed to make the estimates more conservative, and most associations remained significant. The results appeal for strengthened intervention on smoking among HBV-infected population.

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Table 1

Socio-demographic characteristics and major liver cancer risk factors of subjects in Jiangsu liver cancer study 2003–2010 (N = 9,944)

Characteristics	Case		Control		*P* - value
Total	2,011		7,933		
	Mean and SD				
Age (years)	58.7	12.2	63.9	11.4	<0.001
Per capita family income 10 years ago (yuan/RMB)	2,332	2,419	2,204	2,401	0.035
BMI	22.3	3.9	23.1	3.7	<0.001
	Number and proportion %				
Male	1,534	76.3	5,705	71.9	<0.001
Illiteracy	764	38.2	3,796	48.0	<0.001
In marriage	1,717	86.0	6,426	81.5	<0.001
Ever drink alcohol	1,126	56.0	3,679	46.4	<0.001
Have family history of liver cancer	276	13.7	249	3.1	<0.001
HBsAg positive (among 7,712 with serum)	524	43.2	425	6.5	<0.001
Anti-HCV positive	11	0.9	53	0.8	0.751

Table 2

The association between tobacco smoking and liver cancer with semi-Bayes (SB) adjustment in Jiangsu Study 2003–2010 (N = 9,944)

Variables	Case n=2011	Control n=7933	Overall		Male		Female	
			Adjusted OR* (95% CI)	SB-Adjusted OR (95% PI)	Adjusted OR* (95% CI)	SB-Adjusted OR (95% PI)	Adjusted OR* (95% CI)	SB-Adjusted OR (95% PI)
Ever smoke								
No	971	4241	1.00	1.00	1.00	1.00	1.00	1.00
Yes	1040	3692	1.43 (1.20–1.70)	1.42 (1.20–1.69)	1.62 (1.33–1.96)	1.61 (1.32–1.94)	0.82 (0.53–1.26)	0.83 (0.55–1.26)
Smoking status								
Never	971	4241	1.00	1.00	1.00	1.00	1.00	1.00
Former smoker	229	671	1.88 (1.43–2.46)	1.84 (1.41–2.40)	2.19 (1.62–2.96)	2.11 (1.57–2.84)	1.00 (0.47–2.12)	1.00 (0.52–1.94)
Current smoker	703	2609	1.43 (1.19–1.73)	1.42 (1.18–1.71)	1.60 (1.29–1.96)	1.58 (1.29–1.95)	0.89 (0.55–1.46)	0.90 (0.57–1.43)
			$P_{\text{for trend}}<0.001$		$P_{\text{for trend}}<0.001$		$P_{\text{for trend}}=0.200$	
Age at start smoking (years)								
Never smoke	971	4241	1.00	1.00	1.00	1.00	1.00	1.00
45	14	118	1.33 (0.65–2.74)	1.25 (0.66–2.37)	1.01 (0.28–3.56)	1.01 (0.39–2.57)	1.16 (0.49–2.79)	1.11 (0.53–2.32)
35–44	51	211	1.63 (1.00–2.68)	1.54 (0.97–2.46)	1.92 (1.06–3.47)	1.74 (1.01–2.99)	1.06 (0.42–2.67)	1.04 (0.48–2.25)
25–34	262	995	1.47 (1.14–1.89)	1.45 (1.13–1.86)	1.70 (1.29–2.24)	1.67 (1.27–2.18)	0.71 (0.31–1.66)	0.78 (0.38–1.60)
<25	713	2368	1.40 (1.16–1.69)	1.39 (1.15–1.68)	1.57 (1.28–1.94)	1.55 (1.27–1.91)	0.70 (0.39–1.26)	0.74 (0.43–1.27)
			$P_{\text{for trend}}=0.008$		$P_{\text{for trend}}=0.002$		$P_{\text{for trend}}=0.584$	
Daily amount of smoking (cig/day)								
Never smoke	971	4241	1.00	1.00	1.00	1.00	1.00	1.00
<10	104	439	1.81 (1.31–2.50)	1.76 (1.28–2.40)	2.41 (1.68–3.47)	2.28 (1.60–3.24)	0.59 (0.26–1.35)	0.68 (0.33–1.37)
10–19	291	983	1.61 (1.26–2.05)	1.59 (1.25–2.02)	1.75 (1.34–2.29)	1.72 (1.32–2.23)	1.25 (0.66–2.40)	1.20 (0.67–2.16)
20–29	338	1311	1.25 (0.99–1.58)	1.24 (0.99–1.56)	1.40 (1.08–1.81)	1.38 (1.07–1.78)	0.88 (0.44–1.75)	0.90 (0.49–1.67)
30	149	483	1.41 (1.00–1.99)	1.38 (0.99–1.93)	1.65 (1.14–2.38)	1.60 (1.12–2.28)	0.34 (0.04–2.66)	0.72 (0.23–2.29)
			$P_{\text{for trend}}<0.001$		$P_{\text{for trend}}=0.002$		$P_{\text{for trend}}=0.738$	
Duration of smoking (years)								
Never smoke	971	4241	1.00	1.00	1.00	1.00	1.00	1.00
<20	118	309	1.49 (1.04–2.12)	1.45 (1.03–2.05)	1.57 (1.06–2.35)	1.52 (1.03–2.22)	0.84 (0.32–2.25)	0.89 (0.40–1.98)
20–29	239	520	1.76 (1.34–2.32)	1.72 (1.32–2.26)	1.99 (1.47–2.69)	1.93 (1.44–2.59)	0.58 (0.23–1.46)	0.69 (0.32–1.48)
30–39	275	940	1.30 (1.01–1.67)	1.29 (1.01–1.65)	1.41 (1.07–1.85)	1.39 (1.06–1.82)	1.08 (0.53–2.22)	1.06 (0.56–2.01)
40	306	1587	1.42 (1.11–1.81)	1.41 (1.10–1.79)	1.68 (1.28–2.21)	1.65 (1.26–2.15)	0.92 (0.48–1.78)	0.93 (0.52–1.69)
			$P_{\text{for trend}}=0.007$		$P_{\text{for trend}}<0.001$		$P_{\text{for trend}}=0.682$	
Pack-years of smoking			$P_{\text{for trend}}=0.001$		$P_{\text{for trend}}<0.001$			

Variables	Case n=2011	Control n=7933	Overall		Male		Female	
			Adjusted OR* (95% CI)	SB-Adjusted OR (95% PI)	Adjusted OR* (95% CI)	SB-Adjusted OR (95% PI)	Adjusted OR* (95% CI)	SB-Adjusted OR (95% PI)
Never smoke	971	4241	1.00	1.00	1.00	1.00	1.00	1.00
1–19	469	1418	**1.65 (1.34–2.02)**	**1.63 (1.33–2.00)**	**1.88 (1.49–2.37)**	**1.85 (1.47–2.32)**	0.80 (0.47–1.37)	0.82 (0.50–1.36)
20	412	1789	**1.28 (1.01–1.61)**	**1.27 (1.01–1.60)**	**1.45 (1.12–1.87)**	**1.43 (1.11–1.84)**	0.97 (0.51–1.85)	0.98 (0.54–1.75)

*
Adjusted for study area (Dafeng = 1, Ganyu = 2, Chuzhou = 3, Tongshan =4), age (continuous), gender (male = 0, female = 1, except for stratified analyses by gender), education level (illiteracy = 0, primary = 1, middle school = 2, high school and college = 3), marital status (in marriage = 1, single, divorced or widowed = 0), family income 10 years ago per capita (Yuan/year, continuous), BMI (continuous), history of raw water drinking (yes = 1, no = 0), history of mildew-contaminated food intake (yes = 1, no = 0), family history of liver cancer (yes = 1, no = 0), weekly alcohol consumption in 1990s (continuous, mL/week), HBsAg status (positive = 1, negative = 0) and anti-HCV status (positive = 1, negative = 0).

Table 3

Interaction on additive and multiplicative scale between smoking and other risk factors of liver cancer in Jiangsu study, 2003–2010

Factors		case/control	Adjusted OR* (95% CI)	SB-Adjusted OR (95% PI)	Interaction
Ever smoke	HBsAg positive				
No	No	368/3248	1.00	1.00	ROR: 1.64 (1.17–2.30)
No	Yes	229/247	7.66 (6.05–9.71)	7.23 (5.73–9.13)	RERI: 7.77 (3.81–11.73)
Yes	No	321/2826	1.25 (1.03–1.52)	1.24 (1.03–1.51)	AP: 0.50 (0.35–0.64)
Yes	Yes	295/178	15.68 (12.06–20.39)	14.25 (11.01–18.45)	S: 2.12 (1.53–2.94)
Ever smoke	Anti-HCV positive				
No	No	592/3470	1.00	1.00	ROR: 0.62 (0.13–3.05)
No	Yes	6/22	1.55 (0.54–4.44)	1.32 (0.57–3.05)	RERI: −0.61 (−2.93–1.71)
Yes	No	612/2976	1.43 (1.20–1.70)	1.42 (1.20–1.69)	AP: −0.45 (−2.55–1.66)
Yes	Yes	5/31	1.37 (0.41–4.59)	1.20 (0.48–2.97)	S: 0.38 (0.00–43.40)
Ever smoke	Ever drink alcohol				
No	No	651/3128	1.00	1.00	ROR: 0.90 (0.64–1.26)
No	Yes	320/1113	1.88 (1.48–2.38)	1.85 (1.46–2.33)	RERI: 0.08 (−0.47–0.64)
Yes	No	234/1126	1.40 (1.07–1.83)	1.38 (1.06–1.80)	AP: 0.04 (−0.20–0.27)
Yes	Yes	806/2566	2.36 (1.91–2.91)	2.31 (1.88–2.85)	S: 1.07 (0.69–1.64)
Ever smoke	History of raw water drinking				
No	No	370/1990	1.00	1.00	ROR: 1.02 (0.75–1.38)
No	Yes	570/2149	1.36 (1.10–1.68)	1.35 (1.10–1.66)	RERI: 0.19 (−0.24–0.61)
Yes	No	342/1538	1.41 (1.09–1.82)	1.39 (1.08–1.79)	AP: 0.10 (−0.12–0.31)
Yes	Yes	668/2067	1.96 (1.55–2.46)	1.92 (1.53–2.42)	S: 1.24 (0.72–2.14)
Ever smoke	Mildew-contaminated food intake				
No	No	868/3888	1.00	1.00	ROR: 0.91 (0.55–1.50)
No	Yes	84/312	1.28 (0.88–1.87)	1.26 (0.87–1.81)	RERI: −0.05 (−0.78–0.68)
Yes	No	890/3318	1.44 (1.20–1.73)	1.43 (1.19–1.72)	AP: −0.03 (−0.48–0.41)
Yes	Yes	135/334	1.67 (1.18–2.36)	1.62 (1.16–2.27)	S: 0.93 (0.32–2.67)
Ever smoke	Family history of liver cancer				
No	No	849/4121	1.00	1.00	ROR: 1.09 (0.63–1.89)
No	Yes	122/120	3.93 (2.58–6.00)	3.50 (2.34–5.24)	RERI: 1.73 (−0.91–4.37)

Factors		case/control	Adjusted OR[*] (95% CI)	SB-Adjusted OR (95% PI)	Interaction
Yes	No	886/3563	1.42 (1.19–1.69)	1.41 (1.19–1.68)	AP: 0.28 (−0.07–0.64)
Yes	Yes	154/129	6.08 (4.17–8.87)	5.37 (3.73–7.73)	S: 1.52 (0.81–2.84)

[*] Adjusted for study area (Dafeng = 1, Ganyu = 2, Chuzhou = 3, Tongshan =4), age (continuous), gender (male = 0, female = 1), education level (illiteracy = 0, primary = 1, middle school = 2, high school and college = 3), marital status (in marriage = 1, single, divorced or widowed = 0), family income 10 years ago per capita (Yuan/year, continuous), BMI (continuous), history of raw water drinking (yes = 1, no = 0), history of mildew-contaminated food intake (yes = 1, no = 0), family history of liver cancer (yes = 1, no = 0), weekly alcohol consumption in 1990s (continuous, mL/week), HBsAg status (positive = 1, negative = 0) and anti-HCV status (positive = 1, negative = 0), except for in the models for each variable itself.