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Cigarette Smoking And Hepatocellular Carcinoma Risk In Xiamen, China

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Abstract

Recent epidemiologic studies suggest that cigarette smoking may increase the risk of hepatocellular carcinoma (HCC), yet inconsistent dose-response relationships still exist with this association. We examined whether cigarette smoking was associated with HCC risk and explored their dose-response relationship in a case-control study including 590 incident HCC cases and 784 hospital controls in Xiamen, China. Comparisons of HCC cases with hospital controls were conducted for each of the four measures of exposure levels of cigarette smoking - age started smoking, years smoked, cigarettes per day, pack-years in lifetime. After adjustment for demographic factors (sex, age, education, and income level) and alcohol drinking history (lifetime spirit-equivalents intake), no significantly elevated HCC risk was found associated with cigarette smoking in terms of any of these four measures of exposure levels, nor did we demonstrate the dose-response relationship, either in men or in population (women and men together). Comparisons were also conducted for second-hand smoking using “hours of exposure per week” as the measure of exposure levels, but we did not find significant association after adjustment either. Further studies are needed to explore the association between cigarette smoking and HCC risk in this population.

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Introduction

Liver cancer is the sixth most common cancer and the third most common cause of death from cancer worldwide, with an estimated 748,000 new cases and 696,000 deaths in 2008 (Ferlay J, 2010). Nearly 85% of these cases occur in less developed countries, with China alone accounting for more than 50% of the total (Ferlay J, 2010). The estimated age standardized rates (ASRs, per 100,000) of liver cancer incidence in 2008 are 16.0 and 6.0 for men and women respectively (Ferlay J, 2010).

There is wide variation in international liver cancer incidence rates: generally, the highest rates are found in Asia and West and Central Africa, and the lowest in Europe, Oceania, and North America (Jemal A, 2010). International variation in liver cancer rates is largely explained by the distribution of chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, with HBV infection generally dominating in high-risk areas, including Asia and Sub-Saharan Africa, and HCV infection dominating in low-risk areas, including most parts of Europe and North America. Other known risk factors that contribute to the international variations in liver cancer rates include dietary aflatoxin exposure, alcohol-related cirrhosis, fatty liver disease, obesity, and smoking (Chuang SC, 2009).

Liver cancer incidence rates continue to increase in some low-risk parts of the world (Western Europe, North America, and Oceania) whereas they are decreasing in some of the highest risk countries in Asia, based on the analysis of 1993-2002 IARC's Cancer Incidence in Five Continents (CI5) data (Jemal A, 2011). The decrease in Asian countries such as China is thought to reflect reduction in transmission of HBV through improved hygienic and sanitary conditions and reduction in contamination of food with aflatoxins through better food storage system; and infant hepatitis immunization programs implemented over the past two decades have also been shown to decrease the trend in children and adolescents in this area (Jemal A, 2010). Despite this, the incidence rates in Asian countries are still twice as high as those in Africa and more than four times as high as rates in North America (Jemal A, 2011).

The vast majority of primary liver cancers, 75% to 90%, are hepatocellular carcinomas (HCC), which are malignant tumors of liver parenchymal cells (Jemal A, 2011). The most common risk factors include chronic HBV/HCV infection, alcohol intake, and aflatoxin exposure. The risk of HCC in people infected with HBV/HCV is up to 20 times higher than in those who are not (IARC, Hepatitis Viruses, 1994). Both HBV and HCV increase the risk of HCC through their promotion of cirrhosis, although HBV carriers are at risk of HCC even in the absence of cirrhosis (El-Serag HB, 2007). Worldwide, approximately 85% (HBV, 54%; HCV, 31%) of HCC can be attributed to hepatitis virus infection (Parkin, 2006). Other risk factors of HCC include smoking, diabetes, and obesity.

Historically, the primary risk factors for liver cancer in China have been HBV infection and dietary aflatoxin exposure, and these two factors have been shown to have a synergistic effect on HCC (Bosch FX, 2004). Prevention strategies had been implemented to tackle these two risk factors over the past few decades: infant HBV immunization programs, improved sanitary conditions, and reduction in consumption of foods contaminated with aflatoxin, which led to reductions in HCC incidence in China. However, the association between HCC risk and other risk factors such as smoking has not been well established among this population. As HCC development is a multistage process, it is influenced by other environmental and genetic factors, and tobacco use has been suspected as one such candidate (Chen CJ, 1997).

Several constituents of tobacco smoke are known liver carcinogens in humans and experimental animals (Lee YC, 2009). N-Nitrosodimethylamine is carcinogenic in many species including mice, rats and monkeys, and is known to lead to the development of liver tumors (IARC, Some N-Nitroso compounds, 1978). 4-Aminobiphenyl also produces liver tumors in mice. An association between 4-aminobiphenyl–DNA adduct levels in the liver, which were found to be higher in the blood of smokers than of non-smokers, and HCC in Taiwanese patients has been reported (IARC, 1978) (Dooley KL, 1992). Vinyl chloride has been classified as carcinogenic to humans with sufficient evidence for causing angiosarcoma of the liver and HCC (Wang LY, 1998).

Data on smoking as a risk factor for HCC had been conflicting. Early cohort studies from the USA (Hammond, 1966), the Philippines (Basa GF, 1977), Japan (Hirayama, 1989) and China (Tu JT, 1985) reported increased risks of liver cancer among smokers and some evidence of a dose–response relationship (Hirayama, 1989), albeit in some studies this was observed only in HBV carriers (Tu JT, 1985). In 2004, IARC Monograph on tobacco smoke (IARC, Tobacco smoke and involuntary smoking, 2004) concluded that there is now sufficient evidence that tobacco smoking causes liver cancer. However, at about the same time, the US Surgeon General's report on the health consequences of smoking (The health consequences of smoking: a report of the Surgeon General , 2004) concluded that the evidence is suggestive but not sufficient to infer a causal relationship between smoking and liver cancer, mainly because exposures to other risk factors that may act as confounders complicated the evaluation (Lee YC, 2009).

The debate on the associate of smoking and liver cancer seemed to be settled at the end of the first decade of this century. Along with Hepatitis B or C viruses (HBV and HCV) infection, alcohol drinking, and aflatoxin, smoking has been included as the established risk factors of liver cancer (London WT, 2006). A meta-analysis conducted by Gandini et al. on smoking and liver cancer concluded an overall OR of 1.56 (95% CI 1.29–1.87) comparing current-smokers to never-smokers and of 1.49 (95% CI 1.06–2.10) comparing former smokers to never smokers. The associations among current smokers appeared to be consistent with the overall RR regardless of region, study design, study sample size, and publication period (S. Gandini, 2008). A meta-analysis conducted by Lee et al. in 2009 supported the association between cigarette smoking and liver cancer risk. The risk appeared to be moderate, with a ~1.5 fold increase for current smoking, which supported the conclusion by the IARC Monograph (Lee YC, 2009). In 2010, Chuang et al. reported their meta-analysis results that cigarette smoking had a measureable effect on HCC risk, and also suggested a synergistic interaction between cigarette smoking and HBV/HCV infection (Chuang SC, 2010). Recent studies also suggested smoking as a risk factor of HCC. A case-control study nested in a European cohort reported a significant association between cigarette smoking and HCC risk (OR=1.98 for former smoking and OR=4.55 for current smoking) in 2011, and surprisingly an almost 50% attributable risk for smoking, far higher than

the attributable risk of HBV (13%) and HCV (20.9%) infection in population (Trichopoulos D, 2011).

Although the effect of cigarette smoking on the risk of HCC has been established, the dose–response relationship between smoking and HCC risk has been unclear in most epidemiologic studies, particularly, in case–control studies (Tanaka K, 2006). Tanaka et al. reported in 1995 that current, but not former, heavy smoking was an independent risk factor for HCC (RR = 4.9) in a case–control study using hospitalized patients (Tanaka H, 1995). Megumi et al reported in 2008 that no dose–response relationship was evident for pack-years during lifetime, yet more recent cigarette consumption such as pack-years during the last 5 years was significantly associated with HCC risk in a dose-dependent manner in the comparison of HCC cases with Chronic Liver Disease (CLD) patients (Megumi Hara, 2008), and suggested the possibility that a change in recent smoking habit may have a large effect on smoking-HCC relations, thereby distorting dose–response relationships with pack-years during lifetime or cigarette consumption measured in the remote past. A case-control study in the U.S. reported in 2012 that cumulative tobacco use was an independent predictor of HCC risk for patients with chronic liver disease (OR 1.7 for smoking over 11,000 packs of cigarettes over lifetime) (Nghi B. Ha, 2012). In the meta-analysis done by Lee et al in 2009, a positive dose–response trend was observed for the number of cigarettes smoked per day, however, there was substantial heterogeneity for the overall dose–response relationship (Lee YC, 2009). The evidence of heterogeneity disappeared when the dose–response relationship was examined by type of control population. The dose–response relationship for studies with hospital controls was either null or negative, whereas that for studies with population controls was positive (Lee YC, 2009). Thus, type of controls in case–control studies is one likely source of heterogeneity (Lee YC, 2009).

Secondhand smoke is the combination of smoke emitted from the burning ends of a tobacco product (side stream smoke) and the smoke exhaled from the lungs of tobacco users (exhaled mainstream smoke) (Centers for Disease Control, 1986). More than 60 substances contained in second-hand smoke are known or suspected to cause cancer (Environmental Protection

Agency, 1992). Among them, Vinyl chloride has been classified as carcinogenic to humans with sufficient evidence for causing angiosarcoma of the liver and HCC (Wang LY, 1998). Yuan et al. provided evidence demonstrating that side stream smoke, a major component of second-hand smoke, may accelerate the development of experimental non-alcoholic fatty disease (NAFLD) (Yuan H, 2009), a potential risk factor of HCC. However, no direct link has been established between second-hand smoking and liver cancer in epidemiology.

In an attempt to better understand the association between cigarette smoking and the HCC risk, as well as the dose-response relationship between them, we conducted a case-control study in Xiamen, China, to compare the smoking history between HCC cases and hospitals controls. In particular, we are looking at four measures of exposure levels of cigarettes smoking - age started smoking, years smoked, number of cigarettes smoked per day, and pack-years of smoking in lifetime, and one measure of exposure levels of second hand smoke – hours of second hand smoke exposure per week. A better understanding of the magnitude of the effect of cigarette smoking and the dose-response relationship may have important public health message to this area, where the prevalence of smoking and incidence of liver cancer are both high.

Materials and methods

Subjects

HCC cases

Patients with HCC were eligible (i) if primary liver cancer was diagnosed between February 2007 and May 2010, (ii) if they were Chinese and residents of Xiamen City, Fujian Province, China, for at least 10 years. Eligible patients were identified among those who were admitted to Xiamen Hospital of T.C.M, Xiamen University Zhong Shan Hospital, the Third Hospital of Xiamen, or People's Army the 174th Hospital, the four major hospitals in Xiamen City. A total of 620 eligible patients were located, with 590 cases (95.2%) completed participation. The diagnosis of HCC was based on Chinese Society of Liver Cancer Primary Liver Cancer Diagnostic Criteria 2001.

Hospital controls

Controls were recruited from among patients admitted to the spine bone surgical department and the trauma surgical department in the same four hospitals in the same period of time. Control patients were eligible if they were free of tumor and the selection criterion (ii) was met. A total of 850 eligible patients were located, with 784 controls (92.2%) completed participation. The 784 hospital controls were diagnosed as follows: diseases of digestive system (n=74, 9.4%), diseases of genitourinary system (n=92, 11.7%), diseases of musculoskeletal system (n=534, 68.1%), endocrine and metabolic diseases (n=55, 7.0%), diseases of respiratory system (n=7, 0.9%), diseases of blood (n=7, 0.9%), undiagnosed (n=15, 1.9%).

The study protocol was approved by the Institutional Review Board (IRB), and written informed consent to the use of information for this study was obtained from all subjects.

Interviews

Medical staff interviewed recent diagnosed patients in hospitals in person using a standardized questionnaire that requested demographic data, habits of alcohol intake, cigarette use, and second hand smoke exposure one year prior to the interview.

Queries about smoking habit first ascertained current smoking status (ever smoke; if still smoke). We defined "ever smoke" as having been smoking at least one cigarette per day for at least one month, and "still smoke" as still smoking. Then, those who have ever smoked were asked to provide the number of cigarettes they usually smoked per day, age of starting and quitting smoking, and years of smoking. Pack-years of cigarettes in lifetime was calculated as pack-years=number of cigarettes per day*30 days*12 months*years of smoking/7200).

Queries about second hand smoke exposure were first ascertained the current exposure status (exposed to second hand smoke or not). Then, those who have been exposed were asked about how many hours per week they have been in an environment where someone else is smoking.

Queries regarding alcohol use first ascertained current drinking status (ever drink alcohol; if still drink alcohol). We defined "ever drink alcohol" as having been drinking alcohol at least once per month for at least one year, and "still drink alcohol" as still drinking alcohol. Then, those who have ever drunk alcohol were asked to provide their age of starting and quitting drinking, and years of drinking alcohol, and the usual frequency and amount of alcohol use. The amount of alcohol use was reported in Liang (a Chinese unit, which equals to 50 grams) for high-degree Chinese spirit, low-degree Chinese spirit, Chinese yellow or rice wine, red or white wine, champagne or sparkling wine, and beer. Based on the relative alcohol concentration of each drink (Zheng TZ, 1990), we estimated the daily intake of alcohol in spirit-equivalent as high-degree Chinese spirit*1.4, low-degree Chinese spirit *1, Chinese yellow or rice wine/2, red or white wine/3, champagne or sparkling wine/5, and beer/8.

Statistical analysis

Unconditional logistic regression models were used to estimate the odds ratios (ORs) of HCC with their 95% confidence intervals (95% CIs) for cigarette smoking and second-hand smoking with adjustment for potential confounders. Smoking status were determined as never verse ever smokers. Measures of exposure levels of cigarette smoking factors include: age started smoking (never started, started 21+, and started between 1-20 years old); years smoked (0, 1-21, 22-31, and 32+ years); cigarettes per day (0, 1-19, and 20+); pack-years of smoking in lifetime (0, 1-17, 18-31, and 32+). Second hand smoke exposure factors include: exposure

status (unexposed and exposed); hours of exposure per week (0, 1-20, and 21+). Potential confounders include: age (0-39, 40-59, and 60+); sex (female and male); education (0-9 and 10+ school years); annual income (0-18000 and 18001+ RMB); alcohol drinking (0, 1-203, 204-703, and 704+ kilograms of spirit-equivalents intake in lifetime).

The corresponding logistic models were also used to assess the linear trends of HCC risk across exposure levels: ordinal categories of each of the following variables - age started smoking years of smoking, cigarettes per day, pack-years, and hours of second hand smoking per week – were included in the logistic model with covariates respectively.

Among 1374 subjects (590 cases and 784 controls), 50 subjects (18 cases and 32 controls) with smoking related missing data were excluded from the analysis.

As female smokers (n=7 out of 375 subjects) and female subjects exposed to second-hand smoke (n=14 out of 375 subjects) were very few, further analyses were only conducted in population and in men.

Results

Basic characteristics of study subjects

Tables 1.1-1.3 show the basic characteristics of study subjects in population, men, and women respectively. In population, as compared with control group, HCC cases presented higher proportion of males (p<.001), younger subjects (p<.001), lower education level (p<.001), lower annual income (p<.001), drinking alcohol (p<.001), consuming more alcohol during lifetime (p<.001), exposed to second-hand smoking (p<.001) and being exposed with longer hours per week (p<.001), smoking cigarettes (p<.001), younger age started smoking (p<.001), longer years smoked (p<.001), and smoking more cigarettes per day (p<.001) and in lifetime (p<.001). Similar situation was also found in men. In women, since there were only 7 smokers and 14 subjects who had ever been exposed to second hand smoke, further analysis will be not been performed in this group.

Cigarette Smoking

The associations of HCC risk with cigarette smoking for population and for men are explored in Tables 2.1 and Table 2.2, respectively.

In population, before adjustment for demographic factors (sex, age, education level, and annual income) and alcohol drinking (lifetime intake of spirit-equivalents), cigarette smoking showed significantly moderate effect on the HCC risk. Compared to never smokers, the HCC risk was elevated for smokers (OR 1.93, 95% CI 1.55-2.41). In terms of the four measures of exposure levels of cigarettes smoking – age started smoking, years smoked, cigarettes smoked per day, and pack-years, all showed significantly moderate effect on the HCC risk. Compared to never smokers, the HCC risk was elevated for those starting smoking 21+ years old (OR 1.63, 95% CI 1.22, 2.17) and 1-20 years old (OR 2.20, 95% CI 1.69, 2.87), smoking for 1-21 (OR 2.25, 95% CI 1.64, 3.07) and 32+ years (OR 2.89, 95% CI 1.04, 4.08), smoking 1-19 (OR 1.54, 95% CI 1.15, 2.06) and 20+ cigarettes (OR 2.29, 95% CI 1.76, 2.97) per day, and pack-years 1-17 (OR 1.43, 95% CI 1.05, 1.96), 18-31 (OR 2.03, 95% CI 1.49, 2.77) and 32+ (OR 2.59, 95% CI 1.85, 3.62) in

lifetime. All these four measures of levels of exposure showed significant dose-response relationships, with tests for linear trend giving p trend<.001. However, after adjustment for demographics and drinking, the effect of cigarette smoking was not significant any more, and none of the measures of exposure levels showed significant dose-response relationship.

Interestingly, after excluding socioeconomic factors – education and income levels – from the adjustment, the estimated HCC risk changed significantly for some of the measures, giving OR 1.94 (95% CI 1.29-2.91) for years of smoking 32+ and OR 1.71 (95% CI 1.15-2.53) for pack-years 32+, and showing a significant linear trend for pack-year of smoking over lifetime (p trend=.010).

In men, before adjustment for demographic factors (age, education level, and annual income) and alcohol drinking (lifetime intake of spirit-equivalents), the HCC risk was elevated for smokers (OR 1.20, 95% CI 0.92-1.56), however, the effect was not significant. In terms of the four measures of exposure levels of cigarettes smoking, three of them - years smoked, cigarettes smoked per day, and pack-years - showed significantly moderate effect on the HCC risk. Compared to never smokers, the HCC risk was elevated for those smoking for 1-21 (OR 1.47, 95% CI 1.04, 2.08) and 32+ years (OR 1.75, 95% CI 1.20, 2.53), smoking 20+ cigarettes per day (OR 1.38, 95% CI 1.03, 1.86), and pack-years 32+ (OR 1.57, 95% CI 1.09, 2.25). Two measures of levels of exposure showed significant dose-response relationships, with tests for linear trend giving p trend=.034 for cigarettes per day and p trend=.012 for pack-years. However, after adjustment for demographics and drinking, only the highest category of the "years smoked" (32+ years) remained significant (OR 1.56, 95% CI 1.02, 2.39), and none of the measures showed significant dose-response relationship.

After excluding socioeconomic factors – education and income levels – from the adjustment, the estimated HCC risk changed significantly for some of the measures, giving OR 1.42 (95% CI 1.03-1.95) for those smoking 20+ cigarettes per day and OR 1.72 (95% CI 1.16-2.54) for pack-years 32+, and showing significant linear trends across these two measurements (p trend=.033 and .008, respectively).

The influence of socioeconomic status (SES) on the association between cigarette smoking and HCC risk in this population

The multivariate logistic models assessing HCC risk according to pack-years of smoking with adjustment before and after excluding SES factors are shown in Table 2.3 and Table 2.4, respectively. Educational and annual income level seem to play an important role in determining HCC risk in this population, as the adjusted odds ratio of HCC for those having education less than 10 years (compared to 10+ years) is 2.11 (95% CI 1.61-2.76) in population and 1.70 (95% CI 1.27-2.28) in men, and the adjusted odds ratio of HCC for those having annual income less than 18000 RMB (compared to 18001+ RMB) is 2.26 (95% CI 1.73-2.96) in population and 1.87 (95% CI 1.38-2.51) in men. When excluding education and income from this model, the effect of pack-years changed significantly (odds ratio associated with pack-years 32+ is 1.71, 95% CI 1.15-2.53), and test for linear trend became positive (p=.010), suggesting a significant dose-response relationship. Given these results, it seemed that SES factors (education and income) might change the association between cigarette smoking and HCC risk.

To further explore the influence of socioeconomic status on HCC risk, we estimated stratified odds ratios associated with pack-years of smoking with logistic regression. The four strata are as follow: education low/income low, education low/income high, education high/income low, and education high/income high. However, quasi-complete data separation was detected in three of the four strata, in which the odds ratios estimation is questionable. Thus, we did not test heterogeneity of the HCC risk across these four strata; whether or not the SES factors could influence the association between cigarette smoking and HCC risk cannot be determined in this study.

Second-hand smoking

The association of HCC risk with second-hand smoking for population and for men is explored in Tables 3.1 and Table 3.2, respectively.

In population, before adjustment for demographic factors (sex, age, education level, and annual income) and alcohol drinking (lifetime intake of spirit-equivalents), second-hand smoking

showed significantly moderate effect on the HCC risk. Compared to those free from second hand smoking exposure, the HCC risk was elevated for those exposed to second hand smoke (OR 1.81, 95% CI 1.44-2.26). The exposure level – hours per week – showed significant dose-response relationship with test for trend giving p trend <.001. However, the effect was no longer significant after adjustment for demographics and alcohol drinking, and the dose-response relationship was not significant either (p trend =.207). The significance level did not change much after excluding SES factors from the adjustment.

In men, the effect of second-hand smoking was not significant either before or after adjustment for demographics (age, education level, and annual income) and drinking (lifetime intake of spirit-equivalents. The exposure level – hours per week – did not show significant dose-response relationship either before or after adjustment (p trend=.416 and .508, respectively). The significance level for odds ratios and linear trend did not change much after excluding SES factors from the adjustment.

Discussion

In this study, neither cigarette smoking nor second hand smoke exposure significantly elevated the risk of HCC after adjustment for demographics and alcohol drinking, nor had the dose-response relationship been detected. The following points may partly explain the lack of significant results of this study, and are discussed here.

The effect of recent versus remote cigarette smoking habit

Some studies suggested that a change in recent smoking habit may have a large effect on smoking-HCC relationship, thereby distorting dose-response relationships with pack-years during lifetime or cigarette consumption measured in the remote past.

Tanaka et al. in 1995 reported that current, but not former, heavy smoking was an independent risk factor for HCC in a case-control study using hospitalized controls (Tanaka H, 1995). Megumi et al. in 2008 further explored the role of recent smoking habit in HCC development. In the case-control study using both a traditional hospital control group and a chronic liver disease (CLD) patient control group, Megumi et al. demonstrated a significantly increased risk of HCC for current smokers in comparison of HCC cases with CLD controls, but not with hospital controls. Interestingly, the dose-response relationship - in terms of pack-years of smoking in lifetime - was not evident against either control group, but it became clearer for recent cigarette use in comparison of HCC cases with CLD controls: regarding cumulative cigarette consumption during the last 5 years, adjusted odds ratios (and 95% confidence intervals) for 1-4 and 5+ pack-years relative to no use were 1.9 (1.1-3.6) and 2.8 (1.5-5.2) (P trend = 0.003), respectively (Megumi Hara, 2008). Hirayama and Tsukuma et al. also suggested that cigarette smoking may be involved in end-stage development of liver cancer, such as cirrhosis to HCC.

Given these results, cigarette smoking may play a crucial role in the late stage of HCC development, and analysis of the effect of recent smoking habit may be helpful for our study. However, cigarette smoking habits in our study were only recorded in a lifetime-average manner, and information of recent smoking habits was not available. With regard to the HCC risk associated with current versus former smokers, our study gave an unreliable result:

compared to never smokers, the odds ratio of HCC for former smoker is 5.45 (95% CI 2.90-10.24), while for current smoker it is 0.62 (95% CI 0.45-0.85), after adjustment for demographics and alcohol drinking (the data are not reported in the above tables). This discrepancy from general knowledge and literatures on cancer research suggested an obvious influence of the change of behavior due to disease prognosis or diagnosis on the study result. As information of disease stages at the time of quitting smoking (behavior change) was not recorded in our study, the effect of current smoking cannot be identified.

The influence of HBV/HCV infections

Whether or not the association between cigarette smoking and HCC risk would be modified by HBV/HCV infection is still unclear. In the meta-analysis conducted by Chuang et al. in 2010, although a synergistic interaction between cigarette smoking and HBV/HCV infection was suggested, data from individual studies on the interaction between HBV infection and smoking are not consistent (Chuang SC, 2010).

Some studies observed an association between cigarette smoking and HCC only among HBV-negative persons: a case-control study in Hong Kong reported in 1982 that significant association with cigarette smoking was found among primary liver cancer cases who were negative for HBsAg (Lam KC, 1982); a case-control study in Greece reported in 1987 that a statistically significant dose-response relationship of tobacco smoking was found among HBsAg-negative HCC but not among HBsAg-positive HCC cases (Trichopoulos D, 1987); and a cohort study in Taiwan reported in 2003 that HCC risk was significant for cigarette smokers among HBsAg-negatives and there was a significant gradient of HCC risk with the duration of cigarette smoking among HBsAg-negative subjects (Wang LY, 2003).

Some studies reported the association in HBV carriers: a study in Japan reported in 1984 that heavy smoking was found associated with a higher risk of liver cancer among HBsAg-positive subjects (Oshima A T. H., 1984); and a study in Italy reported in 2006 that current smoking was unrelated to HCC risk among HBsAg negatives and anti-HCV negatives, but seemed to enhance the adverse effect of hepatitis virus (S. Franceschi, 2006).

Other studies reported no interaction between smoking and HBV infection: a study in Japan reported in 2000 that there was no significant additive interaction between HBsAg status and a history of cigarette smoking (Mori M, 2000); and a cohort study in Korea reported in 2004 that cigarette smoking and HBV infection were independently associated with increased risk of mortality from HCC but did not interact synergistically (Jee SH, 2004).

By contrast, most studies observed an interaction between cigarette smoking and HCV infection on the risk of HCC (Chuang SC, 2010). Studies in Taiwan (Yu MW, 1991) (Sun CA, 2003), Japan (Hassan MM, 2008), and American (Fujita Y, 2006) reported that cigarette smoking was associated with significantly elevated risk of developing HCC among anti-HCV positive subjects.

Due to the lack of information on HBV/HCV infection in the current stage of our study, we could not verify if HBV/HCV infection would modify the association between cigarette smoking and HCC risk, nor could we explore the synergistic effect of hepatitis virus infection and cigarette smoking in HCC development. If the association between cigarette smoking and HCC risk is indeed dependent on hepatitis virus infection, then it is not unexpected to fail to detect the existence of a significant effect of cigarette smoking on HCC risk or a dose-response relationship in a pooled population consist of individuals with or without hepatitis infections as it is in our study.

Theories were proposed for the role of cigarette smoking in liver carcinogenesis and its potential interaction with viral infection. Cigarette smoke contains several chemicals that are metabolized and activated as carcinogens in the liver (Staretz ME, 1997) 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 (IARC, Hepatitis viruses, 1994). In addition, cigarette smoking may contribute to the progression from chronic HBV and HCV infection to HCC.

The effect of second-hand smoking

The ability of assessing the effect of second-hand smoking of this study was limited: as there are only 13 out of 733 never smoker subjects exposed to second-hand smoking, we did not

estimate the HCC risk associated with second-hand smoking among never smokers; rather, we assessed it among never and ever smokers as a whole. As most subjects who were exposed to second-hand smoking were also exposure to active cigarette smoking, it is difficult to differentiate the effects of these two exposures.

The influence of socioeconomic status (SES)

SES factors – education and income levels – showed independent effects in predicting HCC risk among this population. However, whether the effects of SES would modify the association between cigarette smoking and HCC risk is not clear in this study. Education and income level might partially reflect the awareness of and the potential exposures to HCC risk factors such as dietary aflatoxin, HBV/HCV infection, and other liver diseases, however, none of these factors were captured in the current study. Further investigation is needed to illustrate whether cigarette smoking has effect on HCC risk in this population, whether it exert its effect independently or through interactions with other risk factors.

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Appendix: Tables

Table 1.1 Basic characteristics of study subjects among population

Factors		Population (N=1324)		
		Cases (N=572) n (%)	Controls (N=752) n (%)	p-value*
Sex	Female	88 (15.4)	287 (38.2)	<.001
	Male	484 (84.6)	465 (61.8)	
Age	18-39	60 (10.5)	36 (4.8)	<.001
	40-49	65 (11.4)	89 (11.8)	
	50-59	215 (37.6)	255 (33.9)	
	60-69	167 (29.2)	298 (39.6)	
	>=70	65 (11.4)	74 (9.8)	
Education (years of schooling)	>=10	151 (26.4)	346 (46.0)	<.001
	0-9	421 (73.6)	406 (54.0)	
Annual income (RMB)	>=18,001	138 (24.1)	340 (45.2)	<.001
	0-18,000	434 (75.9)	412 (54.8)	
Smoking status	Never	264 (46.2)	469 (62.4)	<.001
	Ever	308 (53.9)	283 (37.6)	
Age started smoking	Never started	264 (46.2)	469 (62.4)	<.001
	>=21	122 (21.3)	133 (17.7)	
	1-20	186 (32.5)	150 (20.0)	
Years smoked	0	264 (46.2)	469 (62.4)	<.001
	1-21	115 (20.1)	91 (12.1)	
	22-31	89 (15.6)	128 (17.0)	
	>=32	104 (18.2)	64 (8.5)	
Cigarettes/day	0	264 (46.2)	469 (62.4)	<.001
	1-19	115 (20.1)	133 (17.7)	
	>=20	193 (33.7)	150 (20.0)	
Pack-years lifetime	0	264 (46.2)	469 (62.4)	<.001
	1-17	91 (15.9)	113 (15.0)	
	18-31	112 (19.6)	98 (13.0)	
	>=32	105 (18.4)	72 (9.6)	
Second hand smoke exposure	No	315 (55.1)	518 (68.9)	<.001
	Yes	257 (44.9)	234 (31.1)	
Hours of second hand smoke/week	0	315 (55.1)	518 (68.9)	<.001
	1-20	140 (24.5)	115 (15.3)	
	>=21	117 (20.5)	119 (15.8)	
Drinking status	Never	346 (60.5)	563 (74.9)	<.001
	Ever	226 (39.5)	189 (25.1)	
Spirit-equivalents lifetime (kg)	0	346 (60.5)	563 (74.9)	<.001
	1-203	67 (11.7)	34 (4.5)	
	204-703	67 (11.7)	36 (4.8)	
	>=704	65 (11.4)	35 (4.7)	
	Unknown	27 (4.7)	84 (11.2)	

* p-values of $\chi 2$ tests

Table 1.2 Basic characteristics of study subjects among men

Factors		Male (N=949)		
		Cases (N=484) n (%)	Controls (N=465) n (%)	p-value*
Age	30-39	48 (9.9)	29 (6.2)	.025
	40-49	57 (11.8)	67 (14.4)	
	50-59	173 (35.7)	158 (34.0)	
	60-69	145 (30.0)	169 (36.3)	
	>=70	61 (12.6)	42 (9.0)	
Education (years of schooling)	>=10	146 (30.2)	212 (45.6)	<.001
	0-9	338 (69.8)	253 (54.4)	
Annual income (RMB)	>=18,001	129 (26.7)	190 (40.9)	<.001
	0-18,000	355 (73.4)	275 (59.1)	
Smoking status	Never	176 (36.4)	189 (40.7)	.175
	Ever	308 (63.6)	276 (59.4)	
Age started smoking	Never started	176 (36.4)	189 (40.7)	.135
	>=21	122 (25.2)	126 (27.1)	
	1-20	186 (38.4)	150 (32.3)	
Years smoked	0	176 (36.4)	189 (40.7)	<.001
	1-21	115 (23.8)	84 (18.1)	
	22-31	89 (18.4)	128 (27.5)	
	>=32	104 (21.5)	64 (13.8)	
Cigarettes/day	0	176 (36.4)	189 (40.7)	.050
	1-19	115 (23.8)	126 (27.1)	
	>=20	193 (39.9)	150 (32.3)	
Pack-years lifetime	0	176 (36.4)	189 (40.7)	.040
	1-17	91 (18.8)	106 (22.8)	
	18-31	112 (23.1)	98 (21.1)	
	>=32	105 (21.7)	72 (15.5)	
Second hand smoke exposure	No	227 (46.9)	245 (52.7)	.075
	Yes	257 (53.1)	220 (47.3)	
Second hand smoke hours/week	0	227 (46.9)	245 (52.7)	.036
	1-20	140 (28.9)	101 (21.7)	
	>=21	117 (24.2)	119 (25.6)	
Drinking status	Never	258 (53.3)	276 (59.4)	<.060
	Ever	226 (46.7)	189 (40.7)	
Spirit-equivalents lifetime (kg)	0	258 (53.3)	276 (59.4)	<.001
	1-203	67 (13.8)	34 (7.3)	
	204-703	67 (13.8)	36 (7.7)	
	>=704	65 (13.4)	35 (7.5)	
	Unknown	27 (5.6)	84 (18.1)	

* p-values of $\chi 2$ tests

Table 1.3 Basic characteristics of study subjects among women

Factors		Female (N=375)		
		Cases (N=88) n (%)	Controls (N=287) n (%)	p-value*
Age	18-39	12 (13.6)	7 (2.4)	<.001
	40-49	8 (9.1)	22 (7.7)	
	50-59	42 (47.7)	97 (33.8)	
	60-69	22 (4.6)	129 (45.0)	
	>=70	4 (4.6)	32 (11.2)	
Education (years of schooling)	>=10	5 (5.7)	134 (46.7)	<.001
	0-9	83 (94.3)	153 (53.3)	
Annual income (RMB)	>=18,001	9 (10.2)	150 (52.3)	<.001
	0-18,000	79 (89.8)	137 (47.7)	
Smoking status	Never	88 (100.0)	280 (97.6)	.207
	Ever	0 (0.0)	7 (2.4)	
Second hand smoke exposure	No	88 (100.0)	273 (95.1)	.047
	Yes	0 (0.0)	14 (4.9)	
Second hand smoke hours/week	0	88 (100.0)	273 (95.1)	.047
	1-20	0 (0.0)	14 (4.9)	
Drinking status	Never	88 (100.0)	287 (100.0)	-
	Ever	0 (0)	0 (0)	

* p-values of $\chi 2$ tests or Fisher's exact test (when 25% of cells have expected counts less than 5)

Table 2.1 Odds ratios of HCC according to smoking among population

Smoking		Case (N=572)	Control (N=752)	OR (95% CI) Unadjusted	OR^a (95% CI) Adjusted*	OR^b (95% CI) Adjusted**
		n (%)	n (%)			
Smoking status	Never	264 (46.2)	469 (62.4)	1.00	1.00	1.00
	Ever	308 (53.9)	283 (37.6)	1.93 (1.55, 2.41)	0.90 (0.66, 1.21)	1.11 (0.84, 1.47)
Age started smoking	Never	264 (46.2)	469 (62.4)	1.00	1.00	1.00
	>=21	122 (21.3)	133 (17.7)	1.63 (1.22, 2.17)	0.87 (0.62, 1.24)	1.03 (0.73, 1.44)
	1-20	186 (32.5)	150 (20.0)	2.20 (1.69, 2.87)	0.92 (0.65, 1.29)	1.18 (0.85, 1.64)
				p trend<.001	p trend=.616	p trend=.324
Years of smoking	Never	264 (46.2)	469 (62.4)	1.00	1.00	1.00
	1-21	115 (20.1)	91 (12.1)	2.25 (1.64, 3.07)	1.03 (0.70, 1.53)	1.24 (0.85, 1.80)
	22-31	89 (15.6)	128 (17.0)	1.24 (0.91, 1.68)	0.53 (0.36, 0.78)	0.65 (0.45, 0.94)
	>=32	104 (18.2)	64 (8.5)	2.89 (1.04, 4.08)	1.50 (0.98, 2.31)	1.94 (1.29, 2.91)
				p trend<.001	p trend=.856	p trend=.119
Cigarettes/day	Never	264 (46.2)	469 (62.4)	1.00	1.00	1.00
	1-19	115 (20.1)	133 (17.7)	1.54 (1.15, 2.06)	0.72 (0.50, 1.02)	0.85 (0.60, 1.20)
	>=20	193 (33.7)	150 (20.0)	2.29 (1.76, 2.97)	1.08 (0.77, 1.52)	1.36 (0.99, 1.88)
				p trend<.001	p trend=.648	p trend=.064
Pack-years lifetime	Never	264 (46.2)	469 (62.4)	1.00	1.00	1.00
	1-17	91 (15.9)	113 (15.0)	1.43 (1.05, 1.96)	0.61 (0.42, 0.90)	0.76 (0.52, 1.10)
	18-31	112 (19.6)	98 (13.0)	2.03 (1.49, 2.77)	1.03 (0.69, 1.51)	1.12 (0.77, 1.62)
	>=32	105 (18.4)	72 (9.6)	2.59 (1.85, 3.62)	1.23 (0.81, 1.87)	1.71 (1.15, 2.53)
				p trend<.001	p trend=.278	p trend=.010

* OR^a is adjusted for drinking (lifetime intake of spirit-equivalents) and demographics (sex, age, education, income)

** OR^b is adjusted for drinking and demographics, excluding education and income

Table 2.2 Odds ratios of HCC according to smoking among men

Smoking		Case (N=484)	Control (N=465)	OR (95% CI) Unadjusted	OR^a (95% CI) Adjusted*	OR^b (95% CI) Adjusted**
		n (%)	n (%)			
Smoking status	Never	176 (36.4)	189 (40.7)	1.00	1.00	1.00
	Ever	308 (63.6)	276 (59.4)	1.20 (0.92, 1.56)	0.99 (0.73, 1.33)	1.17 (0.88, 1.55)
Age started smoking	Never	176 (36.4)	189 (40.7)	1.00	1.00	1.00
	>=21	122 (25.2)	126 (27.1)	1.04 (.075, 1.44)	0.97 (0.68, 1.37)	1.11 (0.79, 1.56)
	1-20	186 (38.4)	150 (32.3)	1.33 (0.99, 1.79)	1.01 (0.72, 1.42)	1.23 (0.88, 1.70)
				p trend=.061	p trend=.954	p trend=.224
Years of smoking	Never	176 (36.4)	189 (40.7)	1.00	1.00	1.00
	1-21	115 (23.8)	84 (18.1)	1.47 (1.04, 2.08)	1.22 (0.82, 1.82)	1.41 (0.96, 2.08)
	22-31	89 (18.4)	128 (27.5)	0.75 (0.53, 1.05)	0.57 (0.39, 0.84)	0.68 (0.47, 0.98)
	>=32	104 (21.5)	64 (13.8)	1.75 (1.20, 2.53)	1.56 (1.02, 2.39)	1.91 (1.27, 2.86)
				p trend=.150	p trend=.642	p trend=.114
Cigarettes/day	Never	176 (36.4)	189 (40.7)	1.00	1.00	1.00
	1-19	115 (23.8)	126 (27.1)	0.98 (0.71, 1.36)	0.79 (0.55, 1.13)	0.90 (0.64, 1.28)
	>=20	193 (39.9)	150 (32.3)	1.38 (1.03, 1.86)	1.19 (0.85, 1.66)	1.42 (1.03, 1.95)
				p trend=.034	p trend=.301	p trend=.033
Pack-years lifetime	Never	176 (36.4)	189 (40.7)	1.00	1.00	1.00
	1-17	91 (18.8)	106 (22.8)	0.92 (0.65, 1.31)	0.71 (0.48, 1.04)	0.83 (0.57, 1.21)
	18-31	112 (23.1)	98 (21.1)	1.23 (0.87, 1.31)	1.07 (0.73, 1.57)	1.16 (0.80, 1.68)
	>=32	105 (21.7)	72 (15.5)	1.57 (1.09, 2.25)	1.34 (0.89, 2.02)	1.72 (1.16, 2.54)
				p trend=.012	p trend=.138	p trend=.008

*OR^a is adjusted for drinking (lifetime intake of spirit-equivalents) and demographics (age, education, income)

** OR^b is adjusted for drinking and demographics, excluding education and income

Table 2.3 Logistic model for pack-years (with adjustment)

		Population		Male	
Effect		OR (95% CI)	P trend	OR (95% CI)	P trend
Pack-years lifetime	Never	1.00	.278	1.00	.138
	1-17	0.62 (0.42, 0.91)		0.71 (0.48, 1.05)	
	18-31	1.04 (0.71, 1.54)		1.09 (0.74, 1.60)	
	>=32	1.22 (0.80, 1.85)		1.33 (0.88, 2.01)	
Education	>=10	1.00	-	1.00	
(years of schooling)	0-9	2.11 (1.61, 2.76)		1.70 (1.27, 2.28)	
Annual income	>=18,001	1.00	-	1.00	
(RMB)	0-18,000	2.26 (1.73, 2.96)		1.87 (1.38, 2.51)	
Sex	Female	1.00	-	-	
	Male	3.53 (2.50, 4.99)		-	
Age	18-39	1.00	-	1.00	
	40-59	0.54 (0.33, 0.90)		0.63 (0.36, 1.10)	
	>=60	0.49 (0.29, 0.82)		0.68 (0.38, 1.20)	
Spirit-equivalents	0	1.00	-	1.00	
lifetime	1-203	1.88 (1.15, 3.07)		1.95 (1.20, 3.16)	
(kg)	204-703	1.77 (1.14, 2.81)		1.79 (1.14, 2.82)	
	>=704	2.05 (1.26, 3.32)		1.94 (1.21, 3.11)	
	Unknown	0.24 (0.15, 0.40)		0.26 (0.16, 0.43)	

Table 2.4 Logistic model for pack-years (excluding SES factors from adjustment)

		Population		Male	
Effect		OR (95% CI)	P trend	OR (95% CI)	P trend
Pack-years lifetime	Never	1.00	.010	1.00	.008
	1-17	0.76 (0.52, 1.10)		0.83 (0.57, 1.21)	
	18-31	1.12 (0.77, 1.62)		1.16 (0.80, 1.68)	
	>=32	1.71 (1.15, 2.53)		1.72 (1.16, 2.54)	
Sex	Female	1.00	-	-	
	Male	2.86 (2.06, 3.96)		-	
Age	18-39	1.00	-	1.00	
	40-59	0.39 (0.24, 0.63)		0.46 (0.27, 0.79)	
	>=60	0.31 (0.19, 0.51)		0.46 (0.26, 0.79)	
Spirit-equivalents	0	1.00	-	1.00	
lifetime	1-203	1.94 (1.20, 3.12)		1.99 (1.24, 3.20)	
(kg)	204-703	1.93 (1.23, 3.01)		1.92 (1.23, 3.01)	
	>=704	2.00 (1.27, 3.17)		1.93 (1.22, 3.05)	
	Unknown	0.30 (0.19, 0.49)		0.30 (0.19, 0.49)	

Table 2.5 Odds ratios associated with pack-years of smoking, stratified by education and income level, in population

*OR (95% CI) associated with pack-years of smoking	Education 0-9 years		Education 10+ years	
	Income 0-18000 RMB	**Income 18001+ RMB	**Income 0-18000 RMB	**Income 18001+ RMB
Never	1.00	1.00	1.00	1.00
1-17	1.74 (0.94, 3.22)	0.34 (0.11, 1.08)	0.67 (0.31, 1.48)	0.58 (0.01, 0.87)
18-31	1.28 (0.69, 2.38)	0.73 (0.26, 2.01)	2.07 (0.69, 6.24)	0.47 (0.20, 1.13)
>=32	2.03 (1.13, 3.72)	1.60 (0.64, 3.97)	1.05 (0.34, 3.25)	0.14 (0.01, 1.52)

* OR adjusted for sex, age, alcohol drinking (spirit-equivalent in lifetime)

** Quasi-complete data separation detected;

Table 3.1 Odds ratios of HCC according to second-hand smoking among population

Second-hand smoking		**Case (N=572)**	**Control (N=752)**	**OR (95% CI) Unadjusted**	**OR^a (95% CI) Adjusted***	**OR^b (95% CI) Adjusted****
		n (%)	n (%)			
Second hand smoke exposure	No	315 (55.1)	518 (68.9)	1.00	1.00	1.00
	Yes	257 (44.9)	234 (31.1)	1.81 (1.44, 2.26)	0.97 (0.72, 1.30)	1.07 (0.81, 1.42)
Second hand smoke exposure hours/week	None	315 (55.1)	518 (68.9)	1.00	1.00	1.00
	1-20	140 (24.5)	115 (15.3)	2.00 (1.51, 2.66)	1.22 (0.86, 1.74)	1.26 (0.90, 1.77)
	>=21	117 (20.5)	119 (15.8)	1.62 (1.21, 2.16) p trend<.001	0.73 (0.50, 1.06) p trend=.207	0.88 (0.62, 1.26) p trend=.727

*OR^a is adjusted for drinking (lifetime intake of spirit-equivalents) and demographics (sex, age, education, income)

** OR^b is adjusted for drinking and demographics, excluding education and income

Table 3.2 Odds ratios of HCC according to second hand smoke exposure among men

Second hand smoke		**Case (N=484)**	**Control (N=465)**	**OR (95% CI) Unadjusted**	**OR^a (95% CI) Adjusted***	**OR^b (95% CI) Adjusted****
		n (%)	n (%)			
Second hand smoke exposure	No	227 (46.9)	245 (52.7)	1.00	1.00	1.00
	Yes	257 (53.1)	220 (47.3)	1.26 (0.98, 1.63)	1.10 (0.82, 1.48)	1.18 (0.88, 1.58)
Hours of second hand smoke exposure/week	None	227 (46.9)	245 (52.7)	1.00	1.00	1.00
	1-20	140 (28.9)	101 (21.7)	1.50 (1.09, 2.05)	1.47 (1.03, 2.12)	1.49 (1.04, 2.12)
	>=21	117 (24.2)	119 (25.6)	1.06 (0.78, 1.45) p trend=.416	0.81 (0.56, 1.17) p trend=.508	0.93 (0.65, 1.33) p trend=.980

*OR^a is adjusted for drinking (lifetime intake of spirit-equivalents) and demographics (age, education, income)

** OR^b is adjusted for drinking and demographics, excluding education and income