

RESEARCH ARTICLE

Attributable Causes of Liver Cancer Mortality and Incidence in China

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Abstract

Objectives: To estimate the proportion of liver cancer cases and deaths due to infection with hepatitis B virus (HBV), hepatitis C virus (HCV), aflatoxin exposure, alcohol drinking and smoking in China in 2005. **Study design:** Systemic assessment of the burden of five modifiable risk factors on the occurrence of liver cancer in China using the population attributable fraction. **Methods:** We estimated the population attributable fraction of liver cancer caused by five modifiable risk factors using the prevalence data around 1990 and data on relative risks from meta-analyses, and large-scale observational studies. Liver cancer mortality data were from the 3rd National Death Causes Survey, and data on liver cancer incidence were estimated from the mortality data from cancer registries in China and a mortality/incidence ratio calculated. **Results:** We estimated that HBV infection was responsible for 65.9% of liver cancer deaths in men and 58.4% in women, while HCV was responsible for 27.3% and 28.6% respectively. The fraction of liver cancer deaths attributable to aflatoxin was estimated to be 25.0% for both men and women. Alcohol drinking was responsible for 23.4% of liver cancer deaths in men and 2.2% in women. Smoking was responsible for 18.7% and 1.0% . Overall, 86% of liver cancer mortality and incidence (88% in men and 78% in women) was attributable to these five modifiable risk factors. **Conclusions:** HBV, HCV, aflatoxin, alcohol drinking and tobacco smoking were responsible for 86% of liver cancer mortality and incidence in China in 2005. Our findings provide useful data for developing guidelines for liver cancer prevention and control in China and other developing countries.

Keywords: Population attributable fraction - liver cancer - risk factors - China

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Introduction

Liver cancer is the 5th most common cancer in men worldwide, and over 85% of liver cancers occur in developing countries (Ferlay et al., 2010). In China, liver cancer ranks as the 2nd most common cause of cancer death, with mortality rates of 37.5/100,000 in men and 14.4/100,000 in women (Chen et al., 2010). Liver cancer mortality has increased rapidly since the 1970s. Over the past few decades, a number of risk factors for liver cancer have been identified, including hepatitis B virus (HBV), hepatitis C virus (HCV), aflatoxin, alcohol drinking, tobacco smoking, obesity and diabetes (Yu and Yuan, 2004; Chuang et al., 2009). HBV and HCV infection are major risk factors for liver cancer in the Chinese population, reflecting the elevated prevalence of chronic HBV and HCV infection in the general population (Liang et al., 2009).

Several previous studies have estimated the attributable

causes of cancer in western populations (Olsen et al., 1997; International Agency for Research on Cancer et al., 2007; Parkin et al., 2011) and Asian populations (Shin et al., 2011; Inoue et al., 2012; Wang et al., 2012a). For example, one report estimated that HBV and HCV infection, tobacco smoking and alcohol drinking were responsible for 92% of liver cancer deaths in both men and women in Japan in 2005. Only one meta-analysis, reported in a Chinese journal, has estimated the fraction of liver cancer attributable to lifestyle risk factors in China, including HBV, HCV, aflatoxin, smoking, drinking, family history of cancer, and vegetable and fruit intake, but it did not estimate the combined population attributable fraction (PAF) (Yao et al., 2002). We previously conducted a project, aimed at estimating the role of known risk factors of cancer, such as smoking and alcohol drinking, on the cancer burden in China in 2005 (Wang et al., 2012a), which gave us the opportunity to estimate the PAF for relevant risk factors and liver cancer.

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In the present report, we aim to provide an evidence-based assessment of the individual and combined contributions of HBV, HCV, aflatoxin, alcohol drinking and tobacco smoking to the burden of liver cancer deaths and cases in China in 2005.

Materials and Methods

Overview

This report provides an estimate of numbers and proportions [population attributable fractions (PAFs)] of liver cancer deaths and cases in China attributable to HBV, HCV, aflatoxin, alcohol drinking and smoking. Since part of the material (PAF for smoking (Wang et al., 2010), alcohol drinking (Liang et al., 2010), infection (Xiang et al., 2011), and aflatoxin (Liu et al., 2012)) has already been published, this paper focuses on the joint effects of these risk factors on liver cancer and a comparison of these joint effects with those found in other similar studies.

PAF was defined as the proportion of the cancer burden in a population which could be eliminated by modifying or removing the exposure of certain causal factors. We estimated the PAF based on the counterfactual scenario of total avoidance of risk factors (such as smoking and chronic infection). Our estimates were restricted to hepatocellular carcinoma because cholangiocarcinoma is rare in most regions of China and limited data are available at the national level.

Cancer mortality and incidence data

Cancer mortality data were obtained from the 3rd National Death Cause Survey in China (Ministry of Health of the People's Republic of China, 2008). Briefly, this was a retrospective survey conducted in 160 randomly selected counties and 53 areas with high cancer incidence between 2004 and 2005. Liver cancer mortality in our study was estimated based on the 160 randomly selected counties. Cancer incidence data were not available for the entire country; thus, cancer incidence was estimated by using a Mortality/Incidence (M/I) ratio and the mortality data. The M/I ratio was derived from the data of 32 regional population-based cancer registry sites in China between 2003 and 2004, and calculated using Poisson regression adjusted for age, gender and cancer registry site (Chen, 2009).

Exposure data for risk factors of liver cancer in China

The current health effects of risk factors reflect past patterns of exposure to these risk factors (Rothman, 2012). We estimated an average induction time of 15 years for risk factors and liver cancer. Therefore, exposure data were obtained from the early 1990s.

HBV and HCV prevalence: Data on HBV and HCV prevalence were obtained from a nationwide cross-sectional seroepidemiologic study in 1992 (Xia et al., 1996). This study covered 145 disease surveillance points in 30 provinces of China. Approximately 68 000 subjects were investigated using two-stage cluster random sampling. A solid-phase radioimmunoassay was used for detection of hepatitis B surface antigen (HBsAg), antibody to hepatitis B surface antigen (HBsAb), and antibody to

hepatitis B surface antigen (HBsAb); enzyme-linked immunoassay (EIA) was used to detect hepatitis B e antigen (HBeAg); and a second-generation UBI EIA was used to detect antibody to hepatitis C virus.

Aflatoxin prevalence: Few data on aflatoxin exposure are available at the national level. In this report, a published estimate of PAF for aflatoxin in China was abstracted from a worldwide meta-analysis (Liu et al., 2012).

Alcohol drinking prevalence: Data on the prevalence of alcohol drinking were abstracted from the 1991 National Hypertension Survey of China (PRC National Blood Pressure Survey Cooperative Group, 1995), which included 30 provinces, autonomous regions, and municipalities of China. About 949, 539 persons were investigated using a multistage cluster random sampling method.

Smoking prevalence: Data on the prevalence of smoking were derived from the results of two National Smoking Surveys in China in 1984 and 1996. Briefly, in the 1984 national survey, 29 provinces and autonomous regions were covered (Weng et al., 1987). About 519, 600 individuals (including 258, 422 men and 261, 178 women) were investigated using stratified random sampling. The overall smoking prevalence was 33.9% (61.0% in men and 7.0% in women). In the 1996 national survey (Yang et al., 1999), 145 disease surveillance points in 30 provinces of China were included. This population-based survey covered 120, 298 subjects (63, 793 in men and 56, 020 in women) using a 3-stage cluster, random sampling method. The overall smoking prevalence was 37.6% (66.9% for men and 4.2% for women). We estimated the prevalence of smoking in 1990 using a linear interpolation method from the results of these two national surveys.

Relative risk (RR)

To assess the RR of risk factors and liver cancer in the Chinese population, we conducted a systematic search of publications from different sources, including: PubMed, VIP Information, China National Knowledge Infrastructure, and other databases (including Springer, Elsevier, and Science Direct). The search words covered "HBV", "HCV", "hepatitis B virus", "hepatitis C virus", "aflatoxin", "alcohol drinking", "alcohol consumption", "drinking", "tobacco smoking", "smoking", "meta-analysis", "cohort study", "case-control study" and "liver cancer". Studies were included if they included odds ratios or relative risks and corresponding 95% confidence intervals. Meta-analyses and large-scale surveys of representative samples of China were the highest priority. When such studies were not available, we selected non-representative samples of Chinese population studies.

RRs for HBV (Zhou and Fang, 2002), HCV (Zhou and Fang, 2002), alcohol drinking (Pei et al., 2008), were derived from large Chinese meta-analyses, and the RR for aflatoxin came from 5 Chinese studies in a worldwide meta-analysis (Liu et al., 2012). RR for tobacco smoking was obtained from a large case-control study in China (Chen et al., 2003).

RRs for liver cancer incidence or mortality were abstracted separately for men and women; however, RRs

Table 1. Relative Risks (RR) of Selected Risk Factors and Liver Cancer, Which Were Used in the Calculation of Population Attributable Fractions

Risk factors	RR			Source
	Men	Women	Design	
Hepatitis B virus [†]	18.1	18.1	Meta-analysis	Zhou and Fang, 2002
Hepatitis C virus [‡]	13.1	13.1	Meta-analysis	Zhou and Fang, 2002
Alcohol drinking [§]	1.87	1.87	Meta-analysis	Pei et al., 2008
Smoking [¶]	1.36	1.17	Case control study	Chen et al., 2003

[†]RR of liver cancer incidence associated with Hepatitis B virus; [‡]RR of liver cancer incidence associated with Hepatitis C virus; [§]RR of liver cancer incidence associated with alcohol drinking; [¶]RR of liver cancer mortality associated with smoking

were available for both genders in China in only a few studies. Therefore, if the RRs for men and women were not available (such as the RR for HBV or HCV or alcohol drinking), we assumed equal RRs for men and women and used the total RRs as the estimate for both genders.

Statistical analysis

The PAF was calculated based on the relative risk of a risk factor (RR) and the prevalence of exposure to the risk factor in the total population (P) using the following formula, by Levin (Levin, 1953):

$$PAF = \frac{P \times (RR-1)}{[P \times (RR-1)] + 1}$$

The PAF for aflatoxin and liver cancer was abstracted from the results of the Chinese population of a worldwide meta-analysis (Liu et al., 2012). It was estimated based on the proportion of cases exposed (P_c) and the adjusted RR using an alternative formula (Darrow and Steenland, 2011).

$$PAF = \frac{P_c \times (RR-1)}{RR}$$

To estimate the combined PAF for exposure to HBV, HCV, aflatoxin, alcohol drinking and smoking, we used the following formula (Ezzati et al., 2003):

$$PAF = 1 - (1 - PAF_1) \times (1 - PAF_2) \times (1 - PAF_3) \times (1 - PAF_4) \times (1 - PAF_5)$$

where PAF₁ was the PAF for exposure to HBV, PAF₂ was the PAF for exposure to HCV, PAF₃ was the PAF for exposure to aflatoxin, PAF₄ was the PAF for exposure to alcohol drinking, and PAF₅ was the PAF for exposure to smoking. This formula assumes independence of exposure from the five sources.

Table 2. Liver Cancer Deaths and Cases Attributable to HBV, HCV, Aflatoxin Exposure, Drinking and Smoking in China in 2005

Risk factors	Men			Women			Total		
	PAF (%)	Deaths	Cases	PAF (%)	Deaths	Cases	PAF (%)	Deaths	Cases
HBV	65.9	162,646	180,936	58.4	54,020	55,874	63.9	216,666	236,810
HCV	27.3	67,379	74,955	28.6	26,455	27,363	27.7	93,834	102,318
Aflatoxin [†]	25.0	61,702	68,640	25.0	23,125	23,918	25.0	84,827	92,558
Drinking	23.4	51,592	57,794	2.2	1,828	1,890	15.7	53,420	59,684
Smoking	18.7	46,205	51,400	1.0	875	905	13.9	47,080	52,305
Total [‡]	88.4	218,178	242,712	78.4	72,520	75,008	85.7	290,698	317,720

[†]PAF for aflatoxin was obtained from the results of the Chinese population of a meta-analysis (Liu et al., 2012); [‡]Combined PAF for HBV, HCV, aflatoxin, drinking and smoking and liver cancer was calculated using the following formula: PAF=1-(1- PAF₁)×(1- PAF₂)×(1- PAF₃)×(1- PAF₄)×(1- PAF₅); HBV, Hepatitis B virus; HCV, Hepatitis C virus; PAF, Population Attributable Fraction

Results

The number of liver cancer deaths in China in 2005 was 339, 308, including 246, 808 in men and 92, 500 in women, and the number of incident liver cancer cases was estimated to be 370, 236, including 274, 562 in men and 95, 674 in women.

Estimates of prevalence

The prevalence of HBV infection was 11.3% in men and 8.2% in women, and the prevalence of HCV infection was 3.1% in men and 3.3% in women (Xia et al., 1996). The overall prevalence of alcohol drinking was 17.9% (35.1% in men and 2.6% in women) (PRC National Blood Pressure Survey Cooperative Group, 1995). The estimated overall smoking prevalence in 1990 was 35.8% (64.0% in men and 5.6% in women) (Wang et al., 2010).

Estimates of relative risk

For HBV infection, the overall RR was 18.1. For HCV infection, the overall RR was 13.1. For alcohol drinking, the overall RR was 1.87 (95% CI: 1.36-2.57). The RRs for smoking among men and women were 1.36 (95% CI: 1.29-1.43) and 1.17 (95% CI: 1.06-1.29), respectively (Table 1).

PAF calculations

HBV infection contributed to 63.9% of liver cancer deaths and cases, including 65.9% in men and 58.4% in women, respectively. For HCV, the corresponding figures were 27.7% overall, 27.3% among men and 28.6% among women. Liu et al. (2012) estimated the fraction of liver cancer attributable to aflatoxin exposure was 25.0% for both men and women. The proportion of liver cancer attributable to alcohol drinking was 15.7% overall, including 23.4% in men and 2.2% in women. In addition, tobacco smoking was responsible for 13.9% of liver cancer overall, including 18.7% in men and 1.0% in women. Overall, we estimate that 290, 698 (85.7%) of the total liver cancer deaths, including 218, 178 (88.4%) of the deaths in men and 72, 520 (78.4%) of the deaths in women, and 317, 720 incident liver cancer cases (242, 712 in men and 75, 008 in women) in 2005 were attributable to the combined effects of HBV, HCV, aflatoxin, drinking and smoking (Table 2).

Table 3. Comparison of the Population Attributable Fraction (PAF, %) of Liver Cancer Deaths or New Cases Attributable to the Combined Effects of Known Risk Factors

Study	Country	Men	Women	Total
Current study [†]	China	88.4	78.4	85.7
IARC study (International Agency for Research on Cancer et al., 2007) [‡]	France	71.2	43.1	64.4
Parkin et al (Parkin et al., 2011) [§]	UK	48.6	28.0	41.6
Inoue et al (Inoue et al., 2012) [¶]	Japan	92.2	91.8	92.1

[†]PAF of liver cancer was calculated for the combined effects of HBV, HCV, aflatoxin, drinking and smoking; [‡]PAF of liver cancer was estimated for the combined effects of HBV, HCV, drinking and smoking; [§]PAF of liver cancer was estimated for the combined effects of HBV, HCV, ionizing radiation, occupation, drinking and smoking; [¶]PAF of liver cancer was estimated for the combined effects of HBV, HCV, drinking and smoking; HBV, Hepatitis B virus; HCV, Hepatitis C virus

Discussion

This report provides an estimate of the contribution of five known modifiable risk factors to the burden of liver cancer deaths and cases in China in 2005. We estimate that 85.7% of liver cancer deaths in that year were due to the combined effects of HBC, HCV, aflatoxin, alcohol drinking and tobacco smoking. Liver cancer deaths attributable to these risk factors in China represent about 42% of all liver cancer deaths worldwide (Ferlay et al., 2010). Our results may be informative for policies and programs on reducing the burden of liver cancer in China and other developing countries.

We compared our estimates of the combined PAFs with similar estimates published from previous studies in different countries (Table 3). The PAFs in our analysis were much higher than the corresponding figures in France (64.4%) (International Agency for Research on Cancer et al., 2007) and the UK (41.6%) (Parkin et al., 2011), but were comparable with the estimates from Japan (92.1%) (Inoue et al., 2012). HBV and HCV infection are the major risk factors for liver cancer in China, accounting for over 70% of the liver cancer burden. In contrast, in the western populations, HBV and HCV are less important risk factors for liver cancer due to the relatively low prevalence of these infections in these populations.

We estimated that the combined PAF for HBV and HCV infection and liver cancer was nearly 75%, which was comparable with the findings in Korea (74%) (Shin et al., 2011). A more recent global study (de Martel et al., 2012) indicated that 76.9% of incident liver cancer (including cholangiocarcinoma) were attributable to HBV, HCV and liver flukes worldwide, with approximately 88% of cases due to these infections in less developed regions. In China, it has been demonstrated that immunization of infants with a HBV vaccine is beneficial for the primary prevention of HBV infection. HBV infection is the main risk factor of liver cancer in China, so HBV vaccination should greatly reduce the future liver cancer burden. Our results reinforce the idea that control of HBV and HCV infection are an important strategy for reducing the burden of liver cancer mortality and incidence in China.

Aflatoxin has been identified as a carcinogen by the

International Agency for Research on Cancer (IARC) (Baan et al., 2009). China and many other developing nations have both high aflatoxin exposure and high HBV prevalence (Lu et al., 2010). The combined PAF for HBV and aflatoxin exposure in our study was over 70%. Public health strategies for reducing the risk of aflatoxin in the body and the burden of liver cancer can be grouped into three categories: agricultural, dietary and clinical. Agricultural intervention may include planting pest-resistant crops, lowering mold growth in harvested crops, and improving storage methods. Dietary and clinical interventions can be considered secondary interventions. One effective clinical intervention to reduce the burden of aflatoxin-related liver cancer could be HBV vaccination, since there is a multiplicative interaction between aflatoxin and HBV on the risk of liver cancer (Omer et al., 2004; Wu et al., 2009).

Alcohol drinking accounted for 15.7% of liver cancer deaths and cases in China. Boffetta and his colleagues (Boffetta et al., 2006) calculated the burden of cancer deaths and cases attributable to alcohol drinking by WHO sub-region in 2002, and showed that alcohol drinking caused by 9.4% of all liver cancer deaths and cases worldwide. Danaei and colleagues reported that alcohol drinking was responsible for 25% of all liver cancer deaths in seven World Bank regions in 2001 (Danaei et al., 2005). Therefore, our PAF for alcohol was between those reported in previous studies. Alcohol drinking is an especially important risk factor for liver cancer in populations with low prevalence of HBV and HCV, such as the USA and Europe. One potential mechanism for alcohol-related liver carcinogenesis is chronic oxidative stress. As the prevalence of drinking in China is increasing, it is expected that the burden of alcohol related-cancer will increase in the future.

Our estimates for smoking were similar to those reported in previous studies in China (Liu et al., 1998; Gu et al., 2009). Liu and his colleagues (Liu et al., 1998) estimated that smoking contributed to 20.2% of liver cancer deaths among men and 2.4% among women, and Gu and his colleagues (Gu et al., 2009) showed that 20.3% of liver cancer deaths among men and 2.9% among women were attributable to smoking in a prospective study. The corresponding figures in our study were 18.7% for men and 1.0% for women, which were slightly lower than those of the previous studies. The differences in these estimates are related to differences in the RRs, smoking prevalence estimates and methods used for calculating PAFs.

Strengths of our study include the use of nationally-representative data on the prevalence of risk factors, evidence-based data on relative risk of liver cancer, new national data on liver cancer mortality and incidence, and systematic assessment of the burden of liver cancer. Several limitations should also be considered. First, we did not assess the effects of some other known or suspected risk factors, including diabetes and overweight/obesity, because of the lack of appropriate data from China. Recent data indicated diabetes may contribute to the increasing occurrence of liver cancer (Polesel et al., 2009; Yang et al., 2011; Lai et al., 2012; Wang et al., 2012b), and recent meta-analyses show a two-fold increase in the risk of live

cancer among diabetics (Yang et al., 2011; Wang et al., 2012b). If this association is causal, and we assume a prevalence of 2.5%, based on a national survey of diabetes mellitus in the 1990s (Pan et al., 1997), diabetes mellitus was responsible for 2.4% of liver cancer in China in 2005. Evidence also shows that the rapidly growing obesity epidemic may contribute to the rising incidence of liver cancer. The Cancer Prevention study II found that obesity was positively associated with liver cancer deaths in the US population, with an RR of 4.52 among men who had a BMI of 35 kg/m² or above (Calle et al., 2003). If this association is causal and we assume a prevalence among men of 1.0% with a BMI of 35 kg/m² or above, based on the National Nutrition Survey in China in 1992 (Ge, 1997), obesity was responsible for 3.4% of liver cancer among men in China in 2005.

Another limitation of our study was possible uncertainty in the relative risks that we used in making our PAF estimates. The RRs of alcohol drinking and of HBV and HCV were derived from meta-analyses, and some of the original studies included in these meta-analyses may not have been adjusted for confounding factors. Moreover, for alcohol, HBV and HCV, the total RR was used for both genders, and there was uncertainty in the extrapolation of these RRs to categorize each gender individually. A third limitation was that we were not able to find information on the exposure data of aflatoxin in the Chinese population at large, so we were unable to calculate a nationwide PAF for aflatoxin based on data that was as representative of the whole Chinese population as the data on the other exposures that we analyzed. Instead, we abstracted aflatoxin exposure from the results of 5 previous observational studies in China that were reported in a worldwide meta-analysis, and these data may not have been totally accurate for the Chinese population at the national level. Another limitation was that the possible interaction of these risk factors on the risk of liver cancer mortality and incidence was not considered in our estimates because of the lack of available data in China at the national level. But we estimated the joint effects of these risk factors on liver cancer instead. Finally, data on liver cancer incidence in China were not available, and had to be estimated from mortality data and a mortality-to-incidence ratio. This ratio was calculated by Poisson regression models, adjusted for age, gender and cancer registry site, but it was not adjusted for other potentially relevant factors such as socioeconomic status because of unavailable data.

The incidence of liver cancer is approximately three times higher in Chinese men than in Chinese women. Our PAF estimates for the five risk factors combined were 88% in men and 78% in women, which may not differ from each other. If it is true, these would leave some 33,000 cases in men and 21,000 cases in women (in 2005) that cannot be attributed to the five risk factors (i.e., a ratio of about 1.5). This suggests that either the other (suspected and unknown) causes of liver cancer are more important in men than women, or that our gender-specific PAF estimates (based on total rather than gender-specific RRs) are not completely accurate.

In summary, the present results provide a systemic

assessment of the burden of HBV, HCV, aflatoxin exposure, alcohol drinking and tobacco smoking on the occurrence of liver cancer in China. These five modifiable lifestyle risk factors contributed to about 86% of liver cancer deaths and cases in 2005. Our estimates may have implications for policies aimed at liver cancer prevention and control in China and other developing countries.

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