Postprint: Advances in Research on the Epidemiology and Risk Factors of Primary Liver Cancer

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Abstract

Primary liver cancer is one of the most common malignant tumors worldwide, with extremely high incidence and mortality rates. This article details the current epidemiological status of primary liver cancer in China, population attributable fractions, and their associated risk factors. Through searching databases such as PubMed, Web of Science, and China National Knowledge Infrastructure (CNKI), this article finds that hepatitis B virus and hepatitis C virus remain the main risk factors for primary liver cancer. With hepatitis B virus vaccination and antiviral therapy, the incidence of primary liver cancer in China has slightly decreased; however, the incidence of primary liver cancer caused by metabolic factors such as diabetes mellitus, obesity, and non-alcoholic fatty liver disease is gradually increasing; smoking and alcohol consumption are also important risk factors. This article reviews the epidemiological characteristics and risk factors of primary liver cancer, which can provide robust evidence-based medical evidence for formulating prevention and control measures for primary liver cancer.

Full Text

Research Progress in Epidemiology and Risk Factors of Primary Liver Cancer

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Abstract

Primary liver cancer is one of the most common malignant tumors worldwide, with extremely high morbidity and mortality. This article details the current epidemiology of primary liver cancer, population attributable fractions, and associated risk factors in China. Through searches of PubMed, Web of Science, CNKI, and other databases, we found that hepatitis B virus and hepatitis C virus remain the main risk factors for primary liver cancer. With hepatitis B virus vaccination and antiviral treatment, the incidence of primary liver cancer in China has slightly decreased, but the incidence caused by metabolic factors such as diabetes, obesity, and non-alcoholic fatty liver disease is gradually increasing; smoking and alcohol consumption are also important risk factors. This review summarizes the epidemiological characteristics and risk factors of primary liver cancer, which can provide practical evidence-based medical evidence for the development of prevention and control measures for primary liver cancer.

Keywords: Liver neoplasms; Primary liver cancer; Epidemiology; Risk factors; Population attribution fraction; Review

Introduction

Primary liver cancer (PLC) is the sixth most common malignant tumor worldwide and the third leading cause of cancer-related mortality [1]. PLC mainly includes hepatocellular carcinoma (accounting for 75%-85%) and intrahepatic cholangiocarcinoma (accounting for 10-15%). In 2020, there were approximately 905,677 new cases of PLC globally, with deaths reaching as high as 830,180 [1]. The regions with the highest PLC incidence rates are Asia and Africa [2], with the number of PLC patients in China accounting for about half of the global total [3]. Currently, PLC is the fourth most common malignant tumor and the second leading cause of cancer death in China, posing a serious threat to people' s lives and health [4]. Fully understanding the epidemiological characteristics and risk factors of PLC is of great significance for its prevention and treatment. This article reviews the epidemiological features and risk factors of PLC in China, aiming to provide reference and guidance for PLC prevention and control efforts in our country.

1. Literature Search Strategy

A computerized search was conducted of PubMed, Web of Science, CNKI, and other databases from inception to March 2023. Chinese search terms included "primary liver cancer," "epidemiology," "risk factors," and "population attribution fraction," while English search terms included "primary liver cancer," "epidemiology," "risk factors," and "population attribution fraction." Literature unrelated

to the topic, of poor quality, or without full-text availability was excluded, resulting in the inclusion of 64 articles.

2.1 PLC Incidence and Mortality Rates

The age-standardized incidence rate (ASIR) and age-standardized mortality rate (ASMR) of PLC in the Chinese population are 17.81/100,000 and 15.29/100,000, respectively. The total number of annual PLC cases and deaths accounts for approximately half of the global total, with significant urban-rural and regional differences [5]. Specifically, the ASIR (20.07/100,000) and ASMR (17.52/100,000) in rural areas are higher than those in urban populations (ASIR: 16.13/100,000 and ASMR: 13.64/100,000), with the urban-rural difference being particularly pronounced among those under 65 years of age [5]. In terms of geographical distribution, the ASIR and ASMR are highest in the less developed western regions (20.85/100,000 and 16.98/100,000, respectively), followed by the central and eastern regions [5], see Table 1 . Additionally, studies have shown that the ASIR of PLC in China in 2019 decreased by 58.5% compared with 1990, which may be related to the decline in the prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections and aflatoxin exposure [6].

2.2 PLC Demographic Characteristics

PLC incidence is closely related to age [7]. In China, PLC incidence gradually increases with age, remaining low in the <30 years age group, rising rapidly from the $ $30 years age group, and peaking in the 80-84 years age group [8]. Furthermore, the age of PLC onset in China shows an increasing trend over the years. The average age at diagnosis for men in rural and urban areas increased from 56.53 and 59.67 years in 2000 to 61.20 and 62.66 years in 2014, respectively, while for women it increased from 60.60 and 65.50 years to 66.07 and 69.87 years [9]. In most regions worldwide, PLC incidence and mortality rates in men are 2-3 times higher than in women [1]. In China, PLC incidence and mortality are significantly higher in men than in women [8]. This may be related to differences in risk factor exposure between men and women. Studies have found that the prevalence of viral hepatitis, smoking, and alcohol consumption is higher in men than in women [10]. Other research has shown that estrogen/androgen levels are associated with decreased/increased HBV transcription and replication, which may contribute to higher inflammation-driven PLC incidence in men with HBV infection compared with women [11].

2.3 PLC Population Attributable Fraction

The population attributable fraction (PAF) is defined as the burden of cancer in a target population that can be attributed to risk factors [12]. Globally, HBV infection, HCV infection, and alcohol consumption account for 33%, 21%, and 30% of PLC cases, respectively [13]. Due to variations in risk factors across different countries and regions, the PAF also differs. In China, 72.4% of PLC-related

deaths are attributed to risk factors including HBV infection, HCV infection, smoking, alcohol consumption, diabetes mellitus (DM), and obesity [10]. HBV accounts for the largest proportion of the PLC burden in both Chinese men and women; the PAFs for smoking, alcohol consumption, and DM are significantly higher in men than in women; however, the PAF for obesity is higher in women than in men [10], see Table 2 . Additionally, PAF varies across age groups. In men, the PAF for HBV-induced PLC is the largest across all age groups, while the PAFs for smoking- and alcohol-induced PLC show a decreasing trend with age [10]. In women, HBV also has the largest PAF for PLC across all age groups. The PAF for HCV-induced PLC increases with age in both men and women. In the elderly population aged $ $60 years, the PAFs for DM, alcohol consumption, and smoking are higher than in those <60 years [10]. Therefore, actively promoting hepatitis B vaccination, expanding antiviral treatment, and maintaining a healthy lifestyle are the main measures for primary prevention of PLC in China [14].

3. PLC Risk Factors

Common risk factors for PLC include chronic HBV and HCV infection, alcoholic liver disease, and metabolic diseases [such as non-alcoholic fatty liver disease (NAFLD) and DM]. Although antiviral drugs can control and even eradicate chronic HBV and HCV infections to some extent, chronic viral infection remains the main cause of PLC in China. Moreover, with the increasing number of people with obesity and DM, metabolic syndrome (MetS) and NAFLD have become more prevalent, which will further lead to an increase in PLC incidence.

3.1 HBV Infection

HBV infection is an important risk factor for PLC in China. HBV infection can promote PLC development through direct or indirect mechanisms. On the one hand, HBV can induce chromosomal remodeling and abnormal expression of the CTNNB1 oncogene and tumor suppressor genes such as TP53, Axin1, and RB1 through integration or induction of host gene mutations [15]; it can also promote PLC by activating tumor-related signaling pathways [such as the Wnt/β-catenin signaling pathway, phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) signaling pathway, mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) signaling pathway, and oxidative stress pathways] [16], and regulating cellular metabolism (such as glycolysis and fatty acid oxidation) [17]. On the other hand, HBV can alter the liver microenvironment by causing chronic liver inflammation, inhibiting natural killer cell activation, suppressing macrophage secretion of antiviral factors, and overexpressing inhibitory receptors (such as PD-1, CTLA-4, CD244) on virus-specific CD8+ T lymphocytes, thereby promoting viral evasion of immune surveillance and facilitating the progression from inflammation to tumor [16]. According to 2019 Global Burden of Disease data, there were approximately 23,355,000 HBV-infected individuals in China in 2019, with

about 140,000 new cases of HBV-related liver cancer [18]. The lifetime risk of developing PLC in HBV-infected patients is approximately 10%-25% [19]. HBV also synergizes with other risk factors to promote PLC development. A meta-analysis showed that male sex, alcohol consumption, family history of PLC, DM, lack of antiviral treatment, and high HBV DNA replication status are the main risk factors for PLC development in hepatitis B cirrhosis patients [20]. Therefore, HBV vaccination is key to preventing and reducing PLC. Since the implementation of the neonatal HBV vaccination program, the ASIR and ASMR of PLC in China have shown a downward trend [2]. Antiviral treatment is also an effective measure to reduce PLC risk. A meta-analysis showed that antiviral treatment can reduce the risk of PLC (HR=0.189) and cirrhosis (HR=0.347) [21].

3.2 HCV Infection

Multiple mechanisms may contribute to HCV-related carcinogenesis, including inhibition of apoptosis pathways by telomerase activity and HCV core protein, cell cycle dysregulation caused by NS5B, and activation of growth pathways by NS3/4A [22]. In 2019, there were approximately 625,000 HCV-infected individuals in China, with about 34,000 new cases of HCV-related PLC [18]. Once HCV-infected patients progress to the cirrhosis stage, the incidence of PLC is 2%-4% [23]. Sustained virological response achieved through antiviral treatment can significantly reduce the risk of HCV-related PLC [24]. A meta-analysis showed that the incidence of PLC in chronic hepatitis C patients receiving antiviral treatment (1.269/100 person-years) was significantly lower than in untreated chronic hepatitis C patients (3.080/100 person-years) [25]. Currently, in the monitoring guidelines for HCV-related PLC patients, China' s "Guidelines for Stratified Screening and Surveillance of Primary Liver Cancer (2020 Edition)" [26] recommends that patients previously included in PLC surveillance should continue monitoring according to the original plan, as there is currently no reference guide for stopping surveillance.

3.3 Smoking

Cigarettes contain more than 4,000 harmful substances including nicotine, and these tobacco metabolites can bind to DNA to cause gene mutations, increasing the risk of malignant tumors [27]. A prospective study of 500,000 people in China showed that current smokers have a 28% higher risk of developing PLC than never smokers [28]. Research also shows that years of smoking cessation are negatively correlated with PLC risk, with individuals who quit smoking for 30 years having a similar risk of PLC as never smokers [29].

3.4 Alcohol Consumption

Excessive alcohol consumption is a recognized risk factor for PLC [30]. The potential mechanisms by which alcohol and its metabolite acetaldehyde promote PLC include: (1) formation of acetaldehyde and its direct damaging effects on

proteins and DNA; (2) increased production of reactive oxygen species (ROS) induced by cytochrome P450 family 2 subfamily E member 1 and/or iron, with further exacerbation by impaired antioxidant defense and DNA repair mechanisms; (3) induction of chronic inflammation; and (4) interference with methyl transfer and altered gene expression [31]. A meta-analysis showed that the cumulative incidence of PLC in alcohol-related cirrhosis patients at 1, 5, and 10 years of follow-up was 1%, 3%, and 9%, respectively [32]. Heavy drinking ($ $3 drinks/day) increases the risk of PLC in the general population by 16% [33]. Greater alcohol consumption and longer drinking duration are associated with higher risk of PLC [34]. Additionally, the study showed that controlling alcohol consumption and reducing drinking duration can help prevent PLC, especially in people >30 years old and in high-risk populations who should reduce alcohol intake [34]. Furthermore, alcohol synergizes with other risk factors to promote PLC development. A prospective study showed that alcohol consumption and obesity can increase the risk of PLC (HR=3.82) [35]. In patients with alcohol-related cirrhosis, those with DM have a 50% higher risk of developing PLC than those without DM [30]. Therefore, DM screening should be strengthened in heavy drinkers to identify high-risk PLC patients.

3.5.1 Diabetes Mellitus

The potential mechanisms by which DM increases PLC risk include: (1) insulin resistance and excessive lipid accumulation in the liver, causing production of large amounts of free radicals that damage hepatocytes; (2) compensatory hyperinsulinemia causing fatty liver and hepatic fibrosis; and (3) increased secretion of insulin growth factor-1, activating the PI3K/MAPK signal transduction pathway, inducing cell proliferation and inhibiting apoptosis [36]. Studies in different populations show that DM is associated with a 2-3 fold increase in PLC risk, with a significantly higher relative risk in men than in women [37]. A meta-analysis of prospective studies showed that longer duration of DM is associated with increased PLC risk [38]. Additionally, DM is closely related to NAFLD. Research shows that DM is an important metabolic risk factor for NAFLD patients developing PLC [39]. In NAFLD-related cirrhosis patients, the risk of PLC in DM patients is 4.2 times higher than in non-DM patients [40]. A study of 85,000 NAFLD patients with DM with an average follow-up of 10 years showed that patients with DM had a 24% higher risk of developing PLC than those without DM (HR=1.24), and patients with good glycemic control had a 32% lower risk of PLC than those with poor glycemic control (HR=0.68) [41].

3.5.2 Obesity

Obesity promotes PLC development through multiple mechanisms. Exposure of hepatocytes to excessive lipids stimulates oxidative stress and cell damage through different mechanisms [42]. Saturated fatty acids such as palmitate promote PLC by affecting cancer stem cell characteristics, ROS production, and

glucose metabolism [43-44]. Additionally, adipose tissue induced by obesity can secrete various adipokines, leading to insulin resistance and chronic inflammation in different tissues including liver tissue [45]. Obesity can also modulate intrahepatic immunity to induce an immune-tolerant microenvironment [46]. These factors promote the occurrence and development of PLC in obese individuals. A meta-analysis of the general population showed that obesity increases the risk of PLC by approximately 2-fold [47]. A US cohort study showed that individuals with large waist circumference (defined as $ $110 cm in men and $ $90 cm in women) have a 2-fold increased risk of developing PLC [48]. Moreover, obesity can increase PLC occurrence in patients with chronic liver disease. A Chinese study of chronic HBV patients reported that central obesity (defined as waist-to-height ratio >0.5) was associated with increased PLC risk compared with non-central obesity (HR=1.63) [49]. Furthermore, obesity is closely related to NAFLD and together they promote PLC development [50].

3.5.4 NAFLD

The potential mechanisms by which NAFLD increases PLC risk include: (1) various metabolic factors such as obesity and DM cause chronic inflammatory response in the liver, increased lipotoxicity, insulin resistance, and hyperinsulinemia, thereby inducing apoptosis and activating immune and inflammatory pathways, leading to the development of NAFLD and hepatic fibrosis, cirrhosis, and PLC [53]; (2) gut microbiota dysbiosis promotes PLC through mechanisms such as disruption of intestinal mucosal barrier, altered bile acid signaling, and Toll-like receptor activation [54]; and (3) mutations in PNPLA3 cause impaired triglyceride hydrolysis and increased free fatty acid synthesis, promoting PLC development [55]. With the epidemic of obesity and MetS, the incidence of PLC caused by NAFLD is increasing year by year [56]. One study found that the incidence of PLC in NAFLD patients was 0.21/1,000 person-years, significantly higher than in non-NAFLD patients (0.02/1,000 person-years) [57]. Each additional metabolic factor (including DM, obesity, dyslipidemia, and hypertension) increases the risk of PLC in NAFLD patients, with NAFLD patients with DM having a 2.77-fold higher risk of progressing to PLC than non-DM patients [58], suggesting that clinicians should pay attention to PLC screening in NAFLD patients with metabolic factors.

3.6 Other Factors

Aflatoxin is a class of carcinogenic substances produced by Aspergillus flavus and Aspergillus parasiticus, among which aflatoxin B1 (AFB1) is the most toxic and carcinogenic [59]. On the one hand, AFB1 can induce acute hepatic necrosis, leading to cirrhosis or PLC [60]; on the other hand, AFB1 metabolites can bind to DNA through epoxide metabolites and alkylate bases, inducing cell cycle disorders and p53 gene mutations [61], increasing PLC risk. Since 1985, the policy allowing rice to replace corn has reduced aflatoxin albumin adducts by 40-fold, which has contributed to the decline in PLC incidence in China [62].

Microcystin (MC) secreted by cyanobacteria is a class of naturally occurring hepatotoxic metabolites commonly found in freshwater lakes and drinking water. MC mainly induces PLC by inhibiting protein phosphatases 1 and 2A, leading to hyperphosphorylation of intermediate filaments and microfilaments and damage to the hepatocyte cytoskeleton [63]. Studies have shown that cyanobacteria account for less than 1% of the entire oral microbiome, and after adjusting for established PLC risk factors, cyanobacteria were found to be positively associated with PLC [64].

4. Summary and Outlook

Currently, HBV and HCV infections remain the most important risk factors for PLC. With hepatitis B vaccination, effective antiviral treatment for HBV and HCV infected patients, and screening of high-risk populations for viral hepatitis, the prevalence of viral hepatitis will decline. Obesity, DM, NAFLD, and excessive alcohol consumption have gradually become important risk factors for PLC. Promoting healthy lifestyles, strengthening the screening, prevention, and treatment of metabolic diseases such as NAFLD, improving PLC surveillance methods, and continuously refining treatment strategies will effectively improve PLC prevention and control in China, thereby comprehensively reducing the social, economic, and medical burden of PLC in the future. However, there are still urgent research questions and issues to be addressed: (1) there is a lack of specific biomarkers and monitoring methods for early PLC detection; (2) there is a lack of simple stratification tools for identifying high-risk PLC populations, such as self-monitoring apps; and (3) there is a lack of effective treatments for NAFLD. It is hoped that these issues can be resolved in the near future to substantially reduce the global burden of PLC.

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Note: Figure translations are in progress. See original paper for figures.