

Risk Factors for the Development of Hepatocellular Carcinoma in Thailand

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Abstract

Hepatocellular carcinoma (HCC) is the most common type of liver cancer worldwide. The incidence of HCC is on the rise in Thailand, where it has become the most common malignancy in males and the third most common in females. Here, we review some of the risk factors that have contributed to this increase in HCC incidence in the Thai population. Hepatitis B virus (HBV) is the main etiologic risk factor for HCC, followed by hepatitis C virus (HCV). Patients with HBV genotype C have a higher positive rate of hepatitis B early antigen (HBeAg) and progress to cirrhosis and HCC earlier than genotype B. For HCV patients, 16% developed HCC associated cirrhosis by year 5 after diagnosis, and the cumulative risk for death from HCC at year 10 was 60%. Dietary exposure to the fungal hepatocarcinogen aflatoxin B1 has been shown to interact synergistically with HBV infection to increase the risk of early onset HCC. Chronic alcohol abuse remains an important risk factor for malignant transformation of hepatocytes, frequently in association with alcohol-induced cirrhosis. In recent years, obesity and metabolic syndrome have markedly increased the incidence of HCC and are important causes of HCC in some resource-rich regions.

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Introduction

Thailand is a developing country located in Southeast Asia. Laos and Cambodia are to its east, the Gulf of Thailand and Malaysia are to its south, and the Andaman Sea and Myanmar are to its west. The climate of the country as a whole is tropical and characterized by monsoons. According to

Keywords: Risk factors; Hepatocellular carcinoma; Etiology.

Abbreviations: AFB1, aflatoxin B1; ALT, alanine aminotransferase; ASR, age-standardized incidence rate; CHB, chronic hepatitis B; CHC, chronic hepatitis C; DM, diabetes mellitus; HBeAg, hepatitis B virus early antigen; HBsAg, hepatitis B virus surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; IARC, International Agency for Research on Cancer; IGF1, insulin-like growth factor-1; IL-6, interleukin-6; IRS-1, insulin receptor substrate-1; JNK1, c-Jun amino-terminal kinase 1; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; ROS, reactive oxygen species; TNF- α , tumor necrosis factor- α .

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estimates of the National Cancer Register in Thailand, the number of new cancer cases in 2008 was 50,966 males and 51,825 females.¹ These values correspond to age-standardized incidence rates (ASR) of 156.7 per 100,000 for males and 138.2 per 100,000 for females. Liver and bile duct cancer was the most common cancer (ASR=40.6) in males followed by lung and colorectal cancer. In females, breast cancer was the most common (ASR=26.4), followed by cervical cancer and liver and bile duct cancer, as shown in Fig. 1. The annual incidence of liver and bile duct cancer was 40.3 per 100,000 in males and 16.6 per 100,000 in females. In Thailand, liver cancer is the third leading cause of death from malignant neoplasms in males, following lung and stomach cancer. In females, liver cancer ranked fifth as a cause of death during the past decade, following colon, stomach, lung, and breast cancer. Primary liver cancer can be classified into three types, according to the cell from which the cancer originated: hepatocellular carcinoma (HCC), cholangiocarcinoma, and other.

HCC, which is associated with hepatitis B virus (HBV), is a major problem in all regions of Thailand, with the exception of Khon Kaen and the Northeast. Liver flukes, related to cholangiocarcinoma, account for about 89% of all liver cancers in Khon Kaen, which has the highest incidence rate of liver cancer in the world (ASR=97.4 in males and 39.0 in females).² The number of new patients with HCC in Thailand is shown in Table 1. HCC was the first human cancer shown to be amenable to prevention using mass vaccination programs. From a global perspective, the burden of chronic HBV infection is expected to decline because of the increased use of HBV immunization since the early 1980s. National infant vaccination against HBV began in 1992 in Thailand;³ although the number of patients with HCC in the 21st century is greater than that from the 1990s. Vaccine recipients are still too young to have their rates greatly affect the rates in the overall population. Health workers and other high-risk groups are not vaccinated in sufficient numbers. In males, the Thai ASR global ASRs for HCC were 40.3, 42.8, 36.8, and 31.2 in 2008, 2006, 2003, and 1999, respectively. This increase in HCC incidence may be due to several factors, such as improved diagnosis of these patients, better management leading to increased survival, and lower mortality.

Risk factors for HCC

HCC is a complex disease associated with many risk factors and cofactors. The major risk factor for the development of HCC is cirrhosis of the liver, and, not surprisingly, common

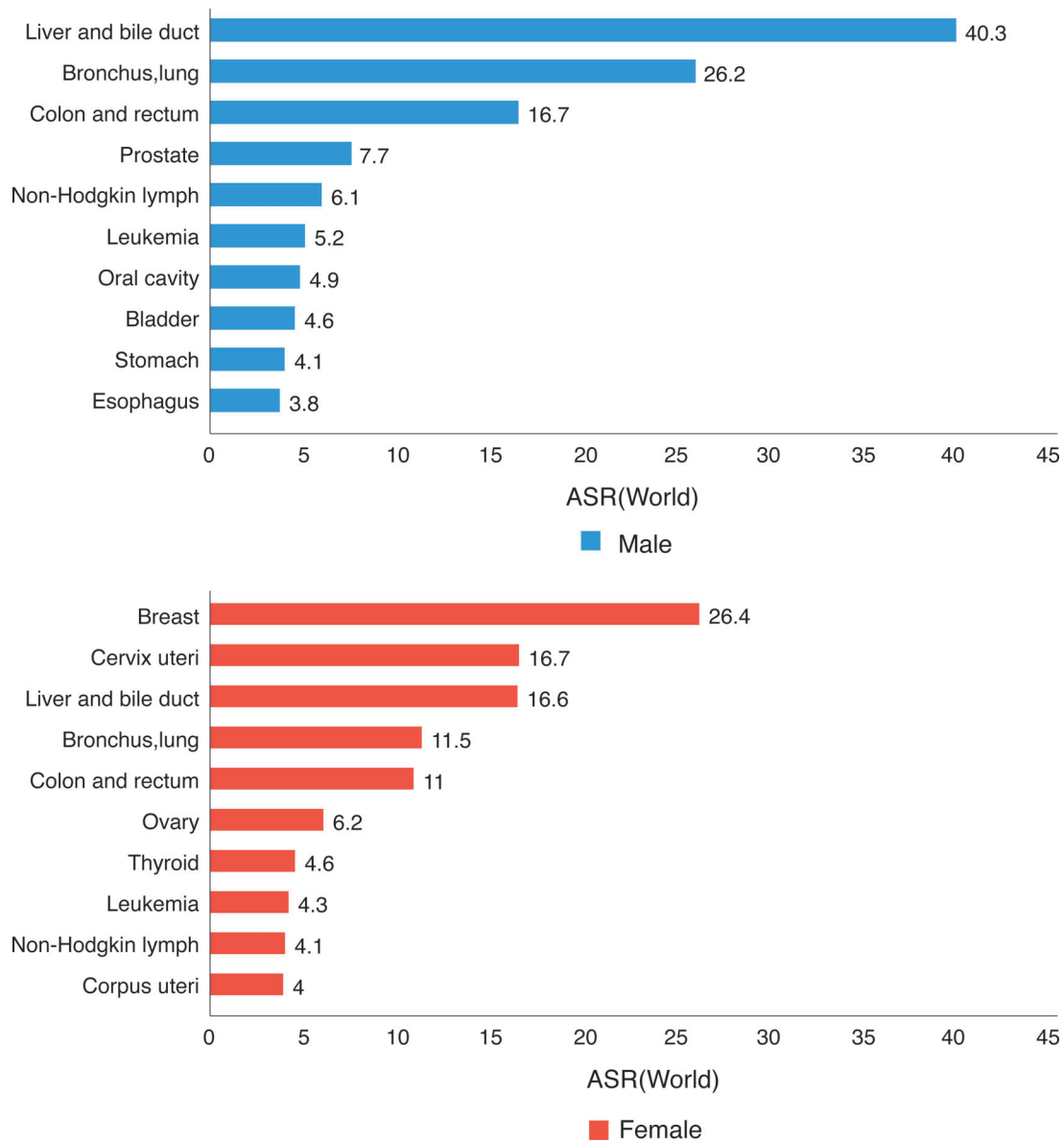


Fig. 1. Leading cancer in Thailand (estimated), 2008.

Table 1. Thailand frequency of new cases of hepatocellular carcinoma

| Year | Total number | Males (ASR, world) | Females (ASR, world) |
|-----------|--------------|--------------------|----------------------|
| 2008 | 19,424 | 13,281 (40.3) | 6,143 (16.6) |
| 2004–2006 | 59,123 | 39,884 (42.8) | 19,239 (18.2) |
| 2001–2003 | 47,439 | 33,313 (36.8) | 14,126 (15.1) |
| 1999 | 11,382 | 8,298 (31.2) | 3,094 (11.5) |

Adapted from Cancer in Thailand.¹ ASR, age-standardized incidence rate.

causes of cirrhosis have been identified as key risk factors for HCC. However, approximately one-quarter of HCC cases diagnosed in Thailand were not linked with any predisposing risk factors. The major known risk factors for HCC can be divided into four categories: viral (chronic hepatitis B and

hepatitis C), toxic (alcohol and aflatoxins), metabolic (diabetes and non-alcoholic fatty liver disease, hereditary hemochromatosis), and immune-related (primary biliary cirrhosis and autoimmune hepatitis). The geographical variability in the incidence of HCC has been attributed to changes

in the natural history and distribution of HBV and hepatitis C virus (HCV) infections. It has been estimated that HBV and HCV are responsible for 50-80% and 10-25%, respectively, of HCC cases worldwide.⁴ In Thailand, the main etiologic risk factor in HCC is HBV,⁵ with a lesser role for HCV.⁶

HBV

The World Health Organization (WHO) has reported that HBV, second only to tobacco, is a human carcinogen. HBV is a DNA hepadnavirus, and it is transmitted by perinatal, parenteral, and sexual exposure. In highly endemic areas, such as Eastern Asia, China, and Africa, approximately 70% of HBV infections are acquired either perinatally or in early childhood.⁷ Perinatal exposure leads to chronic infection in 90-95% of cases, while childhood exposure leads to chronic hepatitis B (CHB) in 50% of cases. The lifetime risk of cirrhosis is 20-30% in perinatal and childhood infections. In low prevalence areas, such as Australia, North America, and Western Europe, HBV is acquired primarily in adulthood through sexual contact or intravenous drug use. Approximately 95% of adults acutely infected with HBV will clear the infection and develop immunity to HBV.⁸ HCC develops in 0.5-0.8% per annum in patients with CHB compared with 1.4-2.5% in those with cirrhosis secondary to CHB.⁹ The annual risk for developing HCC is 0.5% for asymptomatic hepatitis B virus surface antigen (HBsAg) carriers and 0.8% for patients with chronic hepatitis B. Patients with HBV-cirrhosis are at 1000 times greater risk for developing HCC than HBsAg negative individuals.¹⁰ Thus, it appears that the likelihood of acquiring HCC increases as the severity of the underlying liver disease increases. Since most people in Asia with HBV are infected at birth, age on onset of HBV-related cirrhosis is usually earlier than in Western Europe or North America.

There is strong epidemiological data in support of a causal relationship between CHB and HCC. Worldwide, regional variation in the incidence of HCC mirrors the prevalence of CHB in the local population.¹¹ In highly endemic countries with successful immunization programs, such as Taiwan, there has been a decline in both the prevalence of CHB and the incidence of HCC.¹²

HBV factors in HBV-related HCC

The mechanisms underlying carcinogenesis in HBV infection have been extensively studied. A major contributing factor is chronic necroinflammation and subsequent fibrosis and hepatocyte proliferation. In 20% of cases in the developed world and 40% in sub-Saharan Africa and China, however, HCC occurs in noncirrhotic livers.¹³ The contribution of hepatocellular injury and fibrosis in noncirrhotic patients with CHB and HCC is difficult to quantify, but there is evidence that HBV is

directly oncogenic. HBV DNA integrates into the host genome, leading to alterations in cellular signaling and growth control. Both HBV and host hepatocytes may contribute to the final pathogenic outcome, either individually or synergistically. HBV may encode oncogenic viral proteins that contribute to hepatocarcinogenesis. HBV encoded X antigen (HBx) is a viral nonstructural gene that is a multifunctional regulator modulating gene transcription and controlling cell responses to genotoxic stress, protein degradation, apoptosis, and several signaling pathways.¹⁴ The cellular immune response against infected hepatocytes, combined with long-term toxic effects of viral gene products, trigger chronic necroinflammation with subsequent fibrosis and hepatocyte proliferation, increasing the likelihood of malignant transformation.

HBV genotype and viral load in hepatocarcinogenesis

Several viral factors in addition to viral proteins, such as viral genotype and viral load, have been associated with hepatocarcinogenesis. Eight HBV genotypes (A-H) based on genomic sequence divergence have been described. These genotypes have distinct geographical and ethnic distributions: genotypes A and D are found in Africa, Europe, and India; genotype B and C are in Asia; genotype E is found only in West Africa; and genotype F is present in Central and South America. It has been reported that HBV genotype affects clinical outcome and responses to therapy. In Asia, genotype C has been linked to more severe liver disease, cirrhosis, and the development of HCC than genotype B. In Western Europe and North America, genotype D has been associated with more severe liver disease and a higher incidence of HCC than genotype A.¹⁵ The predominant HBV genotypes in Thailand are C and B, accounting for 73% and 21%, respectively. The distribution of genotypes B and C were similar in HCC patients compared to patients with chronic hepatitis or cirrhosis. Patients with genotype C had a higher positive rate of hepatitis B virus early antigen (HBeAg) and exhibited earlier progression to cirrhosis and HCC than genotype B. However, as shown in Table 2, there were no differences in the risk of developing HCC and its prognosis.¹⁶

Serum HBV DNA levels across a biological gradient appear to be a strong predictor for the risk of disease progression and the development of HCC, independent of HBeAg status, serum alanine aminotransferase (ALT) level, and liver cirrhosis.¹⁷ Based on a community survey, it was found that Taiwanese patients were 10 times more likely to develop HCC if HBV DNA was persistently >20,000 IU/mL than if HBV DNA was <2,000 IU/mL. Those patients with a serum HBV DNA titer of 2,000 IU/mL were at increased risk for developing HCC relative to healthy controls.¹⁸

Table 2. Clinical diagnosis of HBV cases

| Diagnosis | N | Sex (M/F) | Age (yr) | HBeAg: positive (%) | Genotype (%) | | | |
|-----------|-----|-----------|-----------|---------------------|--------------|------|------|-----|
| | | | | | A | B | C | U |
| Carrier | 93 | 57/36 | 30.9±10.6 | 51.2 | 2.2 | 17.2 | 78.4 | 2.2 |
| CH | 103 | 84/19 | 36.2±10.1 | 66.3 | 4.9 | 19.4 | 73.8 | 1.9 |
| Cirrhosis | 60 | 47/13 | 48.8±13.8 | 49.1 | 3.3 | 16.7 | 73.3 | 6.7 |
| HCC | 76 | 60/16 | 54.4±12.9 | 21.1 | 2.6 | 30.3 | 65.8 | 1.3 |

Co-infection of HBV and hepatitis D virus (HDV)

HDV co-infection with HBV is associated with increased liver damage. Verme and coworkers showed that HBsAg positive patients with HDV superinfection developed cirrhosis and HCC at an earlier stage (mean age 48 years) compared to HBsAg carrier without HDV infection (mean age 62 years).¹⁹

HCV

HCV is a positive single-stranded RNA flavivirus, and its mode of transmission is predominantly parenteral. Most people infected with HCV (up to 80%) are unable to spontaneously eliminate the virus and progress to chronic hepatitis C (CHC).²⁰ CHC is the causative agent in the majority of HCC in developed countries, where up to 70% of patients with HCC have anti-HCV antibodies in serum.²¹ The risk of HCC in CHC is 1.2-1.7% per annum in patients with underlying chronic hepatitis and 1.4-2.5% per annum in those with cirrhosis.²²

The prevalence of HCV infection varies considerably by geographical region. African and Asian countries have a relatively high prevalence rate compared to North America, Europe, and Australia.²⁰ Egypt has the highest prevalence of HCV in the world (predominantly genotype 4), which has been attributed to previous public health schemes for schistosomiasis.²³ HCV infection rates, up to 60%, have been reported in older individuals who live in rural areas, such as the Nile delta, and in lower social classes.

Several studies have investigated the natural history of HCV infection. In Japan,²⁴ a time lag of 13 years was reported from infection by transfusion of HCV infected blood to the development of chronic hepatitis. This time period was estimated to be 10 years in an American study, where it took about 20 years for the same patients to develop cirrhosis of the liver.²⁵ Development of HCC took 28 years in the American subjects and 29 years in the Japanese cohort. The annual risk for developing HCC depends on the presence and severity of the underlying liver disease.

In HCV infection, viral RNA is not reverse transcribed into DNA, and, thus, it does not integrate into the host genome. In CHC, HCC almost always arises in the setting of cirrhosis. The likely mechanism of hepatocarcinogenesis involves chronic necroinflammation, cellular regeneration, fibrosis, and subsequent progression to cirrhosis, which promotes genomic damage.²⁶ The rate of fibrotic progression following HCV infection is highly variable, as the natural history of the disease typically extends over several decades. Factors that influence the rate of fibrotic progression in HCV-infected patients are age at the time of infection, male gender, HCV

genotype, and alcohol consumption. It remains unclear whether any of these factors affect the onset of liver-related complications by mechanisms other than their effects on the rate of fibrotic progression. To determine which interactive variables were independent determinants of adverse clinical outcomes, Khan and colleagues examined the development of liver-related complications with chronic HCV in a large cohort of patients who were heterogeneous in age, country of birth, mode of HCV acquisition, HCV genotype, and histological and functional severity of liver disease. Patients were followed-up for 5 years. The major independent predictors of liver-related complications identified in this study were sporadic transmission, advanced liver fibrosis at entry, and low albumin.²⁷

The prevalence of HCV in the adult population in Thailand is 2.7% (1.8-3.7%).²⁸ In a long term study greater than 5 years, Punyagupta and colleagues reported that 16% of HCV patients developed HCC associated cirrhosis, which was much a higher percentage than that of HBV, as shown in Table 3. The cumulative risk for death from HCC at year 10 after HCV diagnosis was 60%.²⁹ In Thailand, HCV infection is a major risk factor for the development of HCC.

Combined hepatitis B and hepatitis C

Follow-up studies have shown that patients with combined HCV and HBV infection have a higher risk of developing HCC than those with HCV and HBV alone. The cumulative HCC risk was 10%, 21%, and 23% after 5 years and 16%, 28%, and 45% after 10 years for HCV, HBV, and their combination, respectively.³⁰ The HCC risk in subjects with both infections was investigated in a meta-analysis of 32 epidemiological studies between 1993 and 1997.³¹ The OR for development of HCC in HBsAg positive and anti-HCV/HCV RNA negative subjects was 20.4; in HBsAg negative and anti-HCV/HCV RNA positive subjects, it was 23.6; and in subjects positive for both markers, the OR was 135.0. These data suggested the effect of HBV and HCV co-infection on HCC risk was more than additive. The two viruses may act through both common and distinct pathways in the carcinogenic process. Since HBV acts as a cofactor in the development of HCV related cirrhosis and HCC, vaccination of patients with CHC against HBV has been recommended to avoid additional liver injury.

Coinfection with human immunodeficiency virus (HIV)

The course of CHC is more aggressive in HIV positive subjects, leading to cirrhosis and liver failure in a shorter time period. Co-infection with HIV frequently occurs because

Table 3. The first and final clinical diagnosis of HCV cases

| First clinical diagnosis | N | Late clinical diagnosis | | | |
|--------------------------|----|-------------------------|-----|-----------|------------|
| | | Mild hepatitis | CAH | Cirrhosis | HCC |
| Acute hepatitis | 20 | 9 | 5 | 2 | 4 (20%) |
| Mild hepatitis | 30 | 25 | 3 | - | 2 (6.7%) |
| CAH | 7 | 2 | 3 | - | 2 (28.6%) |
| Cirrhosis | 6 | - | - | 4 | 2 (33.3%) |
| Total | 63 | 36 | 11 | 6 | 10 (15.9%) |

CAH, chronic active hepatitis; HCC, hepatocellular carcinoma.

of shared routes of transmission. A recent study of HCC in HIV-HCV co-infected patients indicated rapid development of HCC in these patients.³²

Alcohol

Consistent with its significant role in cirrhosis, alcohol consumption contributes to 15% to 45% of HCC cases in developed countries.³³ Many studies have demonstrated a significant link between heavy alcohol intake (>50-70 g/d for several years) and HCC,^{34,35} where males tend to consume more alcohol than females. The annual incidence of HCC due to alcohol cirrhosis is 1-4%.³⁶ In contrast to American and European countries, alcohol consumption plays a minor role in HCC development in Asia. This is more true for Middle Eastern countries, where the consumption of alcohol is very low, than southeast Asia.

Role of Aflatoxin AFB1

Aflatoxin exposure is a major risk factor for developing HCC in particular regions where exposure to HBV is endemic. Aflatoxins are fungal toxins produced by *Aspergillus flavus* and *Aspergillus parasiticus*, which can contaminate staple foods, including groundnuts (peanuts). Storage of crops in hot humid conditions can promote the growth and accumulation of aflatoxin-producing fungi. Aflatoxin B1 (AFB1), the most abundant form, is metabolized by P450 enzymes in the liver to generate an epoxide that is highly reactive with DNA, forming adducts at the N7 position of guanine. If this lesion is not repaired, permanent DNA mutations may form, preferentially G to T transversions. A hotspot for AFB1-induced mutations was identified at codon 249 in the TP53 suppressor gene (AGG to AGT, arginine to serine, R249S). Recent evidence confirmed that this position is a preferential site for AFB1 adduct formation.³⁷

In Thailand, the main dietary sources of AFB1 are maize and groundnuts. Individual exposure to AFB1 has been estimated to range from 53 and 73 ng/kg/day, although this figure is likely to vary widely among different geographic areas and ecological zones. The HCC risk attributable to aflatoxin for Thailand was recently shown to be 0.5-0.7 and 15.9-21.9/105 person years in HBsAg-negative and positive subjects, respectively.³⁸ A recent study of a small group of surgically resected HCC patients at the National Cancer Institute, Bangkok reported a R249S mutation in 7/26 (27%) cases, suggesting that the contribution of AFB1 to the burden of HCC in Thailand is far from negligible.³⁹ In contrast, an earlier epidemiological study in Thailand using an albumin-adduct biomarker to assess aflatoxin exposure failed to identify an aflatoxin associated risk for HCC.⁴⁰

Pesticides

Pesticides exposure is one of the environmental factors hypothesized to increase the risk of HCC. Pesticides are considered to be possible epigenetic carcinogens through one or several mechanisms, such as spontaneous initiation of genetic changes, cytotoxicity with persistent cell proliferation, oxidative stress, inhibition of apoptosis, suppression of intracellular communication, and construction of activated receptors.⁴¹

A case-control study of HCC in HBV and/or HCV infected patients from Egypt suggested that pesticides have an

additive effect on HCC risk in rural males, amongst whom the use of carbamate and organophosphate compounds is commonplace.

Metabolic syndrome

A population based study from the United States found diabetes to be an independent risk factor of HCC, regardless of chronic HCV or HBV infection, alcoholic liver disease, or nonspecific cirrhosis. Diabetes was associated with a two- to three-fold increase in HCC risk. About 60% of patients with HCC in this study were not diagnosed with chronic HCV-related or HBV-related hepatitis, alcoholic liver disease, or other known causes of chronic liver disease.⁴² Among these patients, 47% had diabetes, which was higher than those with other risk factors (41%). This suggested that diabetes may represent a considerable proportion of patients with idiopathic HCC. The rising prevalence of obesity and diabetes could be contributing to the increased incidence of HCC in the United States in the past three decades. Moreover, a study in Singapore demonstrated a statistically significant, positive association between diabetes status at baseline and elevated risk of developing HCC among Chinese, a population with relatively high prevalence of HBV infection and HCC incidence.⁴³ This positive diabetes-HCC risk association in individuals without CHB or CHC suggested an independent role of diabetes in HCC development. Also, a Swedish study reported that there is a three-fold increased risk of liver cancer among patients hospitalized with diabetes and a four-fold increased risk in the presence of hepatitis, cirrhosis, and alcoholism.⁴⁴ These findings have important implications in public health, given the worldwide rise in the incidence of type 2 diabetes.

Insulin resistance syndrome in diabetes has been implicated as a risk factor for nonalcoholic fatty liver disease (NAFLD), and nonalcoholic steatohepatitis (NASH) was identified as a cause of cryptogenic cirrhosis and HCC. Emerging evidence has established multiple independent risk factors for the development of HCC, including obesity, diabetes, and iron deposition. These factors also increase the risk for the development of NASH, a probable precursor to cryptogenic cirrhosis. HCC can occur in noncirrhotic as well as cirrhotic NASH patients.⁴⁵ The typical noncirrhotic NASH patient who presents with HCC tends to be older, male, and meets the criteria for one or more features of metabolic syndrome.⁴⁶ The specific sequence of events leading to HCC in the setting of NASH is still under investigation, although certain key events have been determined. Insulin resistance and its subsequent inflammatory cascade that is associated with the development of NASH appear to play a significant role in the carcinogenesis of HCC. Insulin resistance associated with obesity, metabolic syndrome, and diabetes leads to increased release of free fatty acids from adipocytes, release of multiple proinflammatory cytokines (including tumor necrosis factor- α (TNF- α)), interleukin-6 (IL-6), leptin, and resistin and decreased amounts of adiponectin. These processes favor the development of hepatic steatosis and inflammation within the liver.⁴⁷ Hyperinsulinemia may upregulate the production of insulin-like growth factor-1 (IGF1), a peptide hormone that stimulates growth through cellular proliferation and inhibition of apoptosis within the liver.⁴⁸ Insulin also activates insulin receptor substrate-1 (IRS-1), which is involved in cytokine signaling pathways and has been shown to be upregulated in HCC.⁴⁹ The development of NASH is also associated with oxidative stress and the

release of reactive oxygen species (ROS), which likely contributes to the development of HCC. Oxidative stress may favor tumorigenesis through steatosis, inflammation, and cell proliferation, or it may induce cancer-promoting mutations directly. The c-Jun amino-terminal kinase 1 (JNK1) has recently been linked to the development of obesity, insulin resistance, NASH, and HCC. JNK activation is also known to increase hepatic inflammation and apoptosis,⁵⁰ JNK1 appears to be the most important kinase upregulated in HCC.⁵¹

The estimated national prevalence of diabetes in Thai adults was 9.6% (2.4 million people), where 4.8% were previously diagnosed and 4.8% were newly diagnosed.⁵² The rising prevalence of obesity and diabetes could be a contributing factor for the increased incidence of HCC in Thailand over the past three decades.

Conclusions

Like many other developing countries, Thailand is currently undergoing an epidemiologic transition. As urbanization increases, so does environmental exposures and aging and life style changes; and it is likely that the incidence of HCC will continue to rise over the next few years. HBV infection, HBV infection with aflatoxin exposure, viral infection, alcohol consumption leading to overt cirrhosis of the liver, and alcohol consumption leading to cirrhosis of the liver with viral infection are predominant risk factors for the development of HCC in Thailand. The advent of mass-vaccination programs for hepatitis B is beginning to reduce the prevalence rates for HCC. Other possible risk factors of HCC, such as DM and obesity, deserve more attention as the prevalence of these disorders increase worldwide. Our review helps to define the complex etiology of HCC, which may enable policy makers to create targeted and more efficient prevention and screening programs.

Conflict of interest

None

Author contributions

Writing the paper (TC, KP).

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