RESEARCH ARTICLE

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Factors Associated with Hepatocellular Carcinoma among Patients Receiving Treatment at the National Cancer Institute, Thailand: A Case-Control Study

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Abstract

Background: Hepatocellular carcinoma (HCC) is a major public health concern in Thailand, ranking as the leading cause of cancer-related mortality in Thai people. This study aimed to identify various risk factors for HCC among patients treated at the National Cancer Institute (NCI) in Thailand. **Methods:** The retrospective case-control study was conducted using secondary data sources from the Liver Cancer Prevention and Control Research project which was carried out at NCI from 2008 to 2010. A total of 200 cases diagnosed with HCC and 300 healthy controls were included in this study. Univariate analysis and multivariate logistic regression models were used to identify independent risk factors associated with HCC development. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated to quantify the strength and significance of these associations. **Results:** Our analysis showed that the mean ages of cases and controls were 52.2±7.7 years and 53.5±8.2 years respectively. After adjustment for gender, marital status, education, and income, the multivariable logistic regression analysis revealed a statistically significant association between HCC and several other factors. These included hepatitis B virus infection (OR 5.7, 95% CI 2.8-11.6), hepatitis C virus infection (OR 8.2, 95% CI 1.1-60.1) liver cirrhosis (OR 15.7, 95% CI 3.9-63.4), diabetes (OR 3.5, 95% CI 1.5-8.2), alcohol consumption (OR 3.2, 95% CI 1.7-5.9), and smoking status (OR 2.5, 95% CI 1.2-4.9). **Conclusions:** Our findings contribute to the existing knowledge regarding risk factors for HCC among Thai people, particularly highlighting the emerging evidence that associates diabetes with HCC. This study provided baseline information for improving knowledge focused on preventing HCC and avoiding associated risk factors.

Keywords: Hepatocellular carcinoma- risk factors- Thailand

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Introduction

Liver and bile duct cancer is the leading cause of cancer-related death in Thailand. In 2020, there were an estimated 20,000 new cases [1] and almost 16,000 people died from this disease [2]. Most individuals with liver and bile duct cancer are diagnosed at advanced stages, which results in a limitation of their therapeutic options.

In Thailand, hepatocellular carcinoma (HCC) is the most common type of primary liver cancer [3]. The major risk factors for HCC are chronic infections with hepatitis B virus (HBV) and hepatitis C virus (HCV), as well as liver cirrhosis [4]. In addition, lifestyle factors such as excessive alcohol consumption, smoking, and exposure to aflatoxin are recognized contributors to HCC risk [5-6]. Epidemiological evidence also indicates diabetes mellitus and body mass index (BMI), are associated with an increased risk for HCC [7- 8].

Recognizing the considerable public health burden caused by HCC, Thailand has implemented multifaceted strategies to address this issue. In 1992, a nationwide hepatitis B vaccination program for newborns was initiated to reduce the incidence of HCC [9]. Moreover, advancements in medical technology for cancer diagnosis and treatment have also continuously improved, aiming for comprehensive patient care.

However, the effective prevention and control of HCC necessitates a comprehensive understanding of its epidemiology and associated risk factors. In response to these issues, the present study aimed to identify various risk factors associated with HCC among patients receiving treatment at the National Cancer Institute (NCI) in Thailand. The information gleaned from these findings can be used to raise awareness and increase understanding of liver cancer prevention, which will lower the risk of liver cancer among Thai people.

Materials and Methods

Data sources

The present study was an analysis of de-identified secondary data, therefore informed consent from

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individual participants was not required. This study protocol was reviewed and approved by the Ethics Committee of the National Cancer Institute (reference EC COA 047/2021).

The data used in this study were derived from the database of the Liver Cancer Prevention and Control Research, a hospital-based case-control study conducted at the National Cancer Institute in Thailand between 2008 and 2010. The database comprised records of 350 patients aged 24 to 75 years diagnosed with HCC, cholangiocarcinoma, and unknown primary tumors. Additionally, it also included 450 healthy individuals with no history of liver disease or cancer, who attended the annual check-up clinic and were enrolled during the same period. A wide range of variables was recorded for both groups, including demographic information, health behaviors, liver cancer diagnoses, and biochemical test parameters.

Study design and population

This study was a retrospective case-control analysis designed to demonstrate the various risk factors associated with HCC. All study subjects were identified from the database of the Liver Cancer Prevention and Control Research.

Cases were defined as patients aged 30 to 70 years who were diagnosed with HCC in the database between 2008 and 2010. Only patients with confirmed diagnoses of HCC (ICD-10; C22.0) were included in our analysis. Diagnostic confirmation was defined as having a positive diagnosis through a combination of clinical examination, imaging (including ultrasonography, computed tomography, or magnetic resonance imaging), alpha-fetoprotein levels, and liver function tests. Moreover, histological confirmation was obtained through needle biopsies. Standardized and validated methods were employed to evaluate the biochemical data. Patients with clinical diagnoses only or an unknown method of confirmation, as well as those diagnosed with cholangiocarcinoma or unknown primary tumors, were excluded.

Control subjects for this analysis were randomly selected from the same comprehensive database and frequency-matched to HCC case estimates by 5-year age groups to ensure comparability. These controls were defined as healthy individuals with no history of liver disease or cancer diagnoses and were enrolled during the same period as the HCC cases to ensure that they represented the same population and time frame. This helped minimize temporal biases and ensured that any differences between cases and controls were due to the factors being studied rather than external variables linked to the time of enrollment.

The information on independent variables for both HCC cases and controls was also retrieved from the database, comprising clinical characteristics, demographic, and health behavior data. Clinical characteristics included hepatitis virus infection, liver cirrhosis, and a history of diabetes mellitus. These risk factors were based on the clinical presentations documented in the medical records at diagnosis. Diagnosis of viral hepatitis (hepatitis B and C infection) and liver cirrhosis were confirmed by clinicians based on clinical evidence. Other comorbidities included diabetes mellitus (reported history of duration and medications used for diabetes mellitus), and overweight/obesity (body mass index at the time of enrolment). Additionally, demographic and health behavior data, such as age, gender, marital status, educational level, and household income, were included. Alcohol consumption was categorized into three groups [10]: no drinking (0 g/day), moderate drinking (≤50.0 g/day), and heavy drinking (> 50.0 g/day). Smoking status was categorized into three groups: never-smokers, current smokers, and ex-smokers. Body mass index was calculated [(weight (kg)/height (m)2] and classified into four categories: underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), or obese (≥30 kg/m^2).

To ensure data completeness, all cases and controls were screened to confirm the presence of information on relevant risk factors. The analysis also included deceased individuals with complete data on all relevant variables to maximize data utilization. Data cleaning procedures were integrated to identify, and correct errors, as well as remove duplicates or missing data. Observations with incomplete information were excluded from the analysis.

Statistical analysis

Descriptive statistics were used to summarize the characteristics of both study cases and controls. The association between categorical variables was evaluated using either the chi-square test or Fisher's exact test. Conditional logistic regression was performed to estimate the odds ratios (OR) and corresponding 95% confidence intervals (CI) in order to assess the association between various risk factors and the probability of developing HCC. A $p < 0.05$ was considered statistically significant.

Results

In this case-control study, a total of 500 study participants were included, comprising 200 individuals diagnosed with hepatocellular carcinoma (HCC) as cases and 300 healthy controls. Table 1 summarizes the demographic and socioeconomic of case and control groups. The mean (SD) ages of cases and controls were 52.2±7.7 and 53.5±8.2 years, respectively. The majority of cases (84.5%) and controls (73.3%) were male. More than 80% of cases and controls were married. Furthermore, individuals with HCC were more likely to have low household income and limited education compared to controls. The distributions of gender, education, and household income were significantly different between HCC cases and controls.

Table 2 presents the comparisons of various exposure factors between HCC cases and healthy controls. Our findings indicated statistically significant differences in the distribution of chronic hepatitis infection, cirrhosis, diabetes mellitus, BMI, alcohol consumption, and smoking status between individuals diagnosed with HCC and the control group. Among HCC cases, the prevalence of HBV infection was higher at 25.5% compared to controls (8.7%). Similarly, the prevalence of HCV infection was substantially elevated among cases (4.5%) compared

Table 1. Demographic and Socioeconomic Features of HCC Cases and Healthy Controls

Variable	Number (%)		p-value
	Cases (n=200)	Controls (n=300)	
Age (at diagnosis/interview)			
Mean ± SD	52.2±7.7	53.5±8.2	
Gender			
Male	169 (84.5)	220 (73.3)	0.003
Female	31 (15.5)	80 (26.7)	
Marital status			
Single	13 (6.5)	28 (9.3)	0.527
Married	170 (85.0)	247 (82.3)	
Divorced/separated/widowed	17 (8.5)	25 (8.3)	
Education			
No education/Elementary	142 (71.0)	76 (25.3)	<0.001
High School/ College	36 (18.0)	68 (22.7)	
Graduate school	22 (11.0)	156 (52.0)	
Household income (THB)			
0-10,000	120 (60.0)	62 (20.7)	<0.001
10,000-19,999	45 (22.5)	71 (23.7)	
20,000-40,000	23 (11.5)	111 (37.0)	
>40,000	12 (6.0)	56 (18.7)	

Table 2. Prevalence Comparison of Risk Factors in HCC Cases and Healthy Controls

	Number (%)		p-value
	Cases (n=200)	Controls (n=300)	
Viral hepatitis B			
No	149 (74.5)	274 (91.3)	<0.001
Yes	51 (25.5)	26 (8.7)	
Viral hepatitis C			
No	191 (95.5)	298 (99.3)	0.004
Yes	9 (4.5)	2 (0.7)	
Cirrhosis			
No	174 (87.0)	297 (99.0)	<0.001
Yes	26 (13.0)	3 (1.0)	
Diabetes mellitus			
No	172 (86.0)	283 (94.3)	0.001
Yes	28 (14.0)	17 (5.7)	
Body mass index (BMI)			
Normal	95 (47.5)	123 (41.0)	0.004
Underweight	16 (8.0)	7 (2.3)	
Overweight	67 (33.5)	131 (43.7)	
Obese	22 (11.0)	39 (13.0)	
Alcohol consumption			
No drinking	64 (32.0)	183 (61.0)	<0.001
Moderate drinking	42 (21.0)	35 (11.7)	
Heavy drinking	94 (47.0)	82 (27.3)	
Smoking status			
Never-smokers	87 (43.5)	201 (67.0)	<0.001
Current smokers	66 (33.0)	30 (10.0)	
Ex-smokers	47 (23.5)	69 (23.0)	

to controls (0.7%). A higher proportion of HCC cases reported histories of cirrhosis (13%) compared to controls (1%). Also, diabetes mellitus was more frequent among HCC cases (14.0%) than controls (5.7%). Moreover, a significant difference was observed in lifestyle factors, a higher proportion of HCC cases reported being drinkers and current smokers compared to the control group, whereas a larger percentage of controls reported being overweight and obese.

Univariate and multivariate logistic regression analyses were used to identify independent risk factors for HCC (Table 3). Our results demonstrated an association between HCC and various factors. In the multivariable model, we adjusted for potential confounders including gender, marital status, education, and income. Significantly, viral infections emerged as strong independent risk factors. HBV infection was strongly associated with HCC (Adj OR: 5.7, 95% CI: 2.8-11.6). Similarly, HCC cases were almost 8.2 times more likely to have HCV infection than controls (95% CI: 1.1-60.1). Individuals with cirrhosis showed a significantly increased risk of developing HCC, with a 15.7-fold increase in risk (95% CI: 3.9-63.4). Furthermore, those with diabetes mellitus had a 3.5 times higher risk of HCC development (95% CI: 1.5-8.2). In terms of lifestyle factors, heavy alcohol consumption was associated with an increased risk of HCC (Adj OR: 3.2; 95% CI: 1.7-5.9), likewise, current smokers were also found to be at a significantly higher risk of HCC (Adj OR: 2.5; 95% CI: 1.2-4.9). However, our analysis revealed no significant association between BMI and the incidence of HCC.

Discussion

This study aimed to identify various risk factors for hepatocellular carcinoma (HCC) among individuals undergoing treatment at the National Cancer Institute in Thailand. Analysis of the data revealed a predominance of males, comprising more than 80% of the total HCC cases, with a male-to-female ratio of 5:1. This may be because of the sex-specific differences in exposure to the risk factors associated with HCC. For example, males are more likely to engage in behaviors such as alcohol consumption, cigarette smoking, and adopting unhealthy lifestyle habits, all of which are associated with an increased HCC risk. This observation is consistent with those reported by Lampimukhi et al. [11], who also emphasized a higher rate of HCC in men compared to women, which may be due to various environmental and biological factors, including alcohol intake, smoking, and androgen hormone levels. Furthermore, our analysis found that a significant proportion of HCC cases had a low level of education, which suggests a possible link to factors like limited access to healthcare information or lack of awareness and knowledge regarding HCC prevention within this group. As for income levels, most of the HCC

Table 3. Association between HCC and Potential Risk Factors

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	Adj OR [a](95% CI)	p-value
Viral hepatitis B				
No	1		1	
Yes	3.607 (2.16-6.02)	<0.001	5.714 (2.81-11.63)	<0.001
Viral hepatitis C				
No	1			
Yes	7.021 (1.50-32.84)	0.013	8.193 (1.12-60.15)	0.039
Cirrhosis				
No	1		1	
Yes	14.793 (4.41-49.59)	<0.001	15.701 (3.87-63.44)	<0.001
Diabetes mellitus				
No	1		1	
Yes	2.710 (1.44-5.09)	0.002	3.490 (1.49-8.17)	0.004
Body mass index (BMI)				
Normal	1		1	
Underweight	2.959 (1.17-7.48)	0.022	2.596 (0.69-9.74)	0.157
Overweight	0.662 (0.45-0.99)	0.042	0.500 (0.28-0.89)	0.018
Obese	0.730 (0.41-1.31)	0.294	0.905 (0.41-2.01)	0.806
Alcohol consumption				
No drinking	1		1	
Moderate drinking	3.431 (2.02-5.84)	<0.001	2.093 (0.92-4.75)	0.047
Heavy drinking	3.278 (2.17-4.94)	<0.001	3.205 (1.73-5.95)	<0.001
Smoking status				
Never-smokers	1		1	
Current smokers	5.083 (3.08-8.38)	<0.001	2.479 (1.23-4.99)	0.011
Ex-smokers	1.574 (1.01-2.46)	0.047	1.024 (0.52-2.02)	0.946

[a], Adjusted for gender, education, marital status, and household income

cases were associated with lower-income groups, with the majority originating from rural areas (data not shown). These findings indicated the economic barriers individuals encounter in accessing healthcare services, which may lead to delays in diagnosis [12].

In terms of HCC risk factors, our result showed that chronic HBV and HCV infections were significant risk factors for HCC. This finding aligns with studies conducted in various countries [13-15]. Despite the introduction of vaccination against HBV into Thailand's Expanded Program on Immunization (EPI) in 1992, HBV infection persists among middle-aged and older adults. Systematic reviews have estimated the prevalence of HBV in Thailand to range from 4.8-5.1% [16, 17]. Our results also demonstrated a significant association between liver cirrhosis and a higher risk of HCC. In line with a previous meta-analysis that identified cirrhosis as the strongest predictor of both HCC incidence and mortality [18]. Additionally, our study revealed that individuals with a personal history of diabetes mellitus had a 3.5-fold increased risk of developing HCC (95% CI: 1.5-8.2) compared to those without diabetes. Similarly, the risk estimates from numerous studies indicated a statistically significant 1.8-4-fold increased risk of HCC among patients with diabetes [7, 19, 20]. Our finding highlights a potential area for further investigation, as there have been few studies on diabetes mellitus as a risk factor for liver cancer in Thailand. Although the biological mechanism of diabetes mellitus and its associated condition in hepatocarcinogenesis remains incompletely understood, the effect of increased serum insulin levels has been proposed as a potential explanation [21, 22]. Further research is required to clarify the causal role of insulin and other contributing factors in diabetes-associated HCC development.

Several studies have reported obesity was associated with HCC [23, 24]. However, our analysis revealed a lack of significant association between overweight or obese and the risk of HCC. There is a possibility that using BMI at the time of HCC diagnosis, especially in patients with advanced HCC, could result in either underestimation or overestimation of an individual's long-term risk. In this study, our findings indicated that heavy alcohol consumption and current smoking were associated with an increased risk of HCC, consistent with the findings reported in the pooled analysis by Petrick et al. [25]. Moreover, smoking has been reported to increase the risk of development of HCC, particularly among individuals with HCV, and HBV [26].

This case-control study is among the first in Thailand

to investigate the potential association between diabetes and HCC. However, our study has a few limitations. Firstly, the retrospective design of the study needs to be further confirmed by larger prospective and multi-center studies. Secondly, the small sample sizes might not be generalizable to the larger population. Therefore, future work should aim to include a diverse population.

In summary, this study strengthens the existing understanding of HCC risk factors in Thailand. We identify and confirm the established associations with chronic viral infections (HBV, HCV), cirrhosis, and lifestyle factors (alcohol consumption and smoking). In addition, our finding contributes to the expanding amount of data that indicates the association between diabetes mellitus and HCC in Thailand. This study provided important baseline information for improving community education on HCC prevention. It can be used to develop and implement strengthened prevention strategies, ultimately reducing the incidence and burden of HCC.

Author Contribution Statement

SS conceptualized and initiated the study design. PP designed the analytical approach, performed the statistical analysis, interpreted the data, and drafted the manuscript under the supervision of SS.

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Ethics approval

All procedures performed in the present study were approved by the Ethics Committee of the National Cancer Institute (reference EC COA 047/2021).

Approval

This study was approved by the Ethics Committee of the National Cancer Institute in Thailand. It was not conducted as part of a student thesis.

Data Availability

The database analyzed during the present study is not publicly available but can be obtained from the corresponding author upon reasonable request and with ethical approval.

Conflict of interest

The authors declared no conflict of interest for this study.

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