Effects of Alcohol Consumption and Hepatitis History on the Association between Gender and Cirrhosis

ผลของการดื่มแอลกอฮอล์ และโรคไวรัสตับอักเสบต่อความสัมพันธ์ของเพศกับโรคตับแข็ง

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ABSTRACT

The male gender is reported as a common association with liver cirrhosis (LC) especially who drink alcohol. However, various studies attest a stronger association between women and LC. Furthermore, studies investigating the factors associated to women diagnosed with LC have yet to be performed. Therefore, this study aims to identify factors associated with LC in men and women. Multiple logistic regression was used to analysis indicated that gender difference in LC was associated with alcohol consumption. Women who consumed alcohol associated with LC less than men 76% (OR = 0.24; 95% CI: 0.18 to 0.33; p-value <0.001) and non-alcohol drinking woman also associated with LC less than men 51% (OR = 0.49; 95%CI: 0.35 to 0.68; p-value<0.001). Women who has hepatitis history and non-hepatitis history associated with LC less than men 76% and 71% respectively (OR = 0.24; 95%CI: 0.18 to 0.33; p-value<0.001), (OR = 0.29; 95%CI: 0.12 to 0.69; p-value<0.005). Therefore, alcohol drinking women and hepatitis history women have higher associated with LC than women who not drink and who not hepatitis history.

บทคัดย่อ

จากการศึกษาที่ผ่านพบว่าเพศชายมีแนวโน้มการตายจากโรคตับแข็งมากกว่าเพศหญิง ในขณะเดียวกันก็มีการศึกษาที่พบว่า เพศหญิงก็มีความสัมพันธ์กับการเกิดโรคตับแข็ง ด้วยเหตุนี้ความสัมพันธ์ระหว่างเพศกับการเกิดโรคตับแข็งจึงยังไม่ชัดเจน ผู้วิจัยจึงมีความสนใจที่จะศึกษาความสัมพันธ์ระหว่างเพศ กับโรคตับแข็ง วิเคราะห์ข้อมูลโดยใช้สถิติการถดถอยพหุลอจิสติก เพื่ออธิบายเพื่ออธิบายผลของการดื่มแอลกอฮอล์และประวัติโรคไวสรัสตับอักเสบต่อความสัมพันธ์ระหว่างเพศกับการเกิดโรคตับแข็ง พบว่าในเพศหญิงที่ดื่มแอลกอฮอล์มีโอกาสเกิดโรคตับแข็งน้อยกว่าเพศชายร้อยละ 76 (OR = 0.24; 95% CI: 0.18 ถึง 0.33; p-value <0.001) และผู้หญิงที่ไม่ดื่มแอลกอฮอล์มีโอกาสเกิดโรคตับแข็งน้อยกว่าเพศชายร้อยละ 51 (OR = 0.49; 95%CI: 0.35 ถึง 0.68; p-value<0.001) สำหรับผู้หญิงที่มีประวัติโรคไวรัสตับอักเสบและไม่มีประวัติโรคไวรัสตับอักเสบมีโอกาสเกิดโรคตับแข็งน้อยกว่าเพศชายร้อยละ 76 และร้อยละ 71 ตามลำดับ (OR = 0.24; 95%CI: 0.18 ถึง 0.33; p-value<0.001), (OR = 0.29; 95%CI: 0.12 ถึง 0.69; p-value<0.005) ดังนั้นเพศหญิงที่ดื่มแอลกอฮอล์และมีประวัติโรคไวรัสตับอักเสบมีโอกาสเป็นโรคตับแข็งมากกว่าเพศหญิงที่ไม่ดื่มแอลกอฮอล์และไม่มีประวัติเป็นโรคไวรัสตับอักเสบ

Keywords: Gender, Alcohol consumption, Liver cirrhosis

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Introduction

Liver cirrhosis (LC) is a major contributor to the global health burden, with more than 1 million deaths reported in 2010 (Mokdad et al., 2014). In 2009, the National Center for Health Statistics (NCHS) and Centers for Disease Control (CDC) ranked LC as the 12th leading cause of death overall and the 5th leading cause of death for patients aged 45 to 54 years old (Heron, 2012). LC is associated to scar tissue formation that can progress to bile duct cancer also known as cholangiocarcinoma (CCA) (Hui et al., 2003). Central Europe ranks LC among the top 14 most common causes of death in adults (Blachier, Leleu, Peck-Radosavljevic, Valla, & Roudot-Thoraval, 2013; Hoyert & Xu, 2012; Lozano et al., 2012). African and Asian countries report high numbers of afflicted LC patients with co-morbidities of chronic hepatitis B virus (HBV) infections (Perz, Armstrong, Farrington, Hutin, & Bell, 2006; Seeff & Hoofnagle, 2006) with particularly high incidences of LC and liver cancer being reported in Thailand, which was the major public health problem (Poovorawan et al., 2015) (Ferlay et al., 2010).

LC is an advanced stage of liver fibrosis that accompanied by distortion of the hepatic vasculature which is the chronic consequence of chronic liver diseases (CLD) characterized and diagnosed by ultrasonography (US) parenchymal patterns (Pinzani, Rosselli, & Zuckermann, 2011; Schuppan & Afdhal, 2008). US is the technique used to diagnose various liver disorders including LC (Allan, Thoirs, & Phillips, 2010). It is inexpensive, non-invasive, readily available, and an efficient means for health screening which could be detected morphologic changes in the liver enabling the early detection of liver cancer (Bruix, Sherman, & American Association for the Study of Liver, 2011; Soresi, Giannitrapani, Cervello, Licata, & Montalto, 2014). US specifically projects parenchymal echo patterns used by radiologists to diagnose LC (Kimura, Ebara, Ohto, & Kondo, 1989). Recently, studies utilizing US have produced novice information regarding the diagnosis and progression of CLD (Berzigotti & Piscaglia, 2011; Claudon et al., 2013; Soresi et al., 2014).

The major causes of LC include alcohol abuse, HBV, hepatitis C virus (HCV), diabetes mellitus (DM) and being male (Horie, Yamagishi, Ebinuma, & Hibi, 2013). Multiple studies investigating LC found stronger associations between the male gender and LC than females including higher mortality rates (Rogers, Everett, Onge, & Krueger, 2010; Scaglione et al., 2015). However, other studies report women having a stronger association with LC than men (Corrao, Arico, Zambon, Torchio, & Di Orio, 1997; M. d. T. a. T. Poynard, 2003). Therefore, this study aims to identify the factors associated to men and women diagnosed with LC in Northeast Thailand.

Objectives of the study

To determine the effect of alcohol and hepatitis history with LC in Northeast Thailand.

Methodology

Study design

This study was a cross-sectional study that took place from 2013 to 2015. The study utilized data from the Cholangiocarcinoma Screening and Care Program (CASCAP), a prospective cohort study regarded as the first project

for CCA screening in a high-risk population at the community level in Khon Kaen Province, Northeast Thailand (Khuntikeo et al., 2015).

Study population

A total of 108,529 subjects were enrolled in the CASCAP project in 2013. All subjects were from Northeast Thailand and were 40 years old or over. Figure 2 illustrates the process of sample selection. Our study included 60,108 subjects who were diagnosed with LC based on ultrasonography screenings performed by CASCAP radiologists.

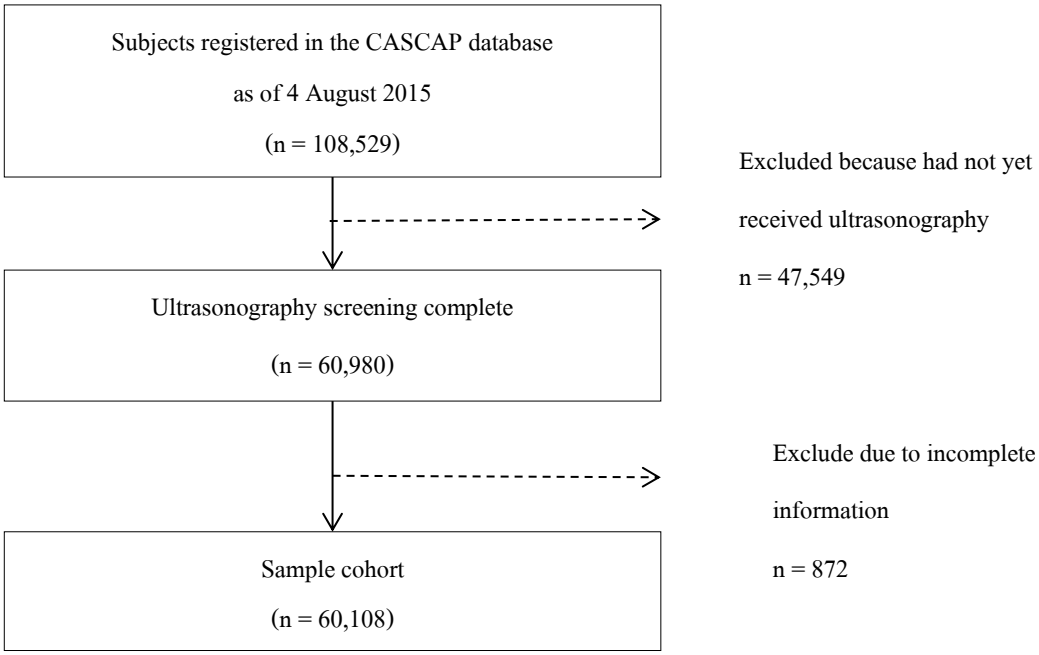

Figure 1 Sample selection process

Factors used to characterize the subjects

Demographic characteristics of study subjects included gender, age, education, occupation, smoking history, alcohol consumption, HBV infection, and diabetes mellitus (DM). These factors are considered biologically and sociologically relevant in demonstrating a relationship with LC.

Data analysis

Demographic characteristics were described using frequencies and percentages for categorical data such as gender, age group, education, occupation, smoking history, alcohol consumption, HBV, and DM. The continuous data such as the actual age of subjects were analyzed using the mean, standard deviation (SD), median, minimum, and maximum values.

The prevalence of LC was calculated and the percentages were computed based on a normal approximation of a binomial distribution. Simple logistic regression was used to investigate factors associated with LC, as determined by crude odds ratios (ORs) and their 95% confidence intervals (CIs). Then we performed a multiple

logistic regression to determine factors independently associated with LC and were presented by adjusted ORs and their 95% CIs. This analysis was adjusted for the factors indicated above.

All test statistics were two-tailed and a p-value of less than 0.05 was considered statistically significant. All analyses were performed by using STATA version 10 (StataCorp, 2007).

Results

A total of 60,108 subjects were included in our study with a mean age of 54.9 (±9.33). There were more female participants than male participants (57.9% and 42.1%, respectively). The majority of our study participants completed primary school (74.2%) and worked as farmers (79.4%) (Table 1).

Table 1 Demographic characteristics of subjects presented as numbers and percentages

Characteristics	Male	n(%)	Female	n(%)	Total	n (%)
Overall	25,294	(42.1)	34,814	(57.9)	60,108	(100)
Age						
40 to 49	6,659	(29.6)	11,419	(36.9)	18,078	(33.8)
50 to 59	8,373	(37.2)	11,278	(36.5)	19,651	(36.8)
60 to 69	5,407	(24)	6,131	(19.8)	11,538	(21.6)
70+	2,086	(9.3)	2,094	(6.8)	4,180	(7.8)
Mean(±SD)		55.8(±9.46)		54.3(±9.17)		54.9 (±9.33)
Median (min: max)		54.9 (40:99.3)		52.9 (40:98.9)		53.7 (40:99.3)
Education						
None	178	(0.7)	359	(1.0)	537	(0.9)
Primary	18,095	(72.2)	26,068	(75.7)	44,163	(74.2)
Secondary (M1-M6)	4,541	(18.1)	5,421	(15.7)	9,962	(16.7)
Certificate	444	(1.8)	511	(1.5)	955	(1.6)
Bachelor +	1,789	(7.1)	2,094	(6.1)	3,883	(6.5)
Occupation						
Unemployed	403	(1.6)	1,072	(3.1)	1,475	(2.5)
Famer	20,079	(80.2)	27,179	(78.8)	47,258	(79.4)
Labor	1,499	(6.0)	1,908	(5.5)	3,407	(5.7)
Own business	718	(2.9)	1,110	(3.2)	1,828	(3.1)
Government official	1,834	(7.3)	1,968	(5.7)	3,802	(6.4)
Other	509	(2.0)	1,239	(3.6)	1,748	(2.9)
Smoking						
No	11,935	(48.0)	33,339	(97.4)	45,274	(76.6)

Table 1 Demographic characteristics of subjects presented as numbers and percentages (Cont.)

Characteristics	Male	n(%)	Female	n(%)	Total	n (%)
Yes	12,944	(52.0)	879	(2.6)	13,823	(23.4)
Alcohol consumption						
No	7,237	(28.9)	25,186	(73.2)	32,423	(54.5)
Yes	17,786	(71.1)	9,235	(26.8)	27,021	(45.5)
Hepatitis B history						
No	24,641	(97.4)	34,230	(98.3)	58,871	(97.9)
Yes	653	(2.6)	584	(1.7)	1,237	(2.1)
Hepatitis C history						
No	25,242	(99.8)	34,763	(99.8)	60,005	(99.8)
Yes	52	(0.2)	51	(0.2)	103	(0.2)
Diabetes mellitus						
No	24,292	(96)	32,867	(94.4)	57,159	(95.1)
Yes	1,002	(4.0)	1,947	(5.6)	2,949	(4.9)

The overall prevalence of LC was 0.8% and more common in men than women, 1.3% and 0.4% , respectively. The prevalence of LC steadily increased with age but declined with increasing levels of education. The highest prevalence of LC occurred in those diagnosed with HCV (4.9%) (Table 2).

Gender was presented as a statistically significant factor in regards to LC. Women demonstrated a less than 70% association to LC when compared to men (OR = 0.30; 95% CI: 0.25 to 0.37; p-value <0.001). Other factors that were significantly associated with LC included: older age, having a smoking history, consuming alcohol, HBV infection, and DM diagnosis. The number of those diagnosed with HCV was low, therefore, did not present statistical significance.

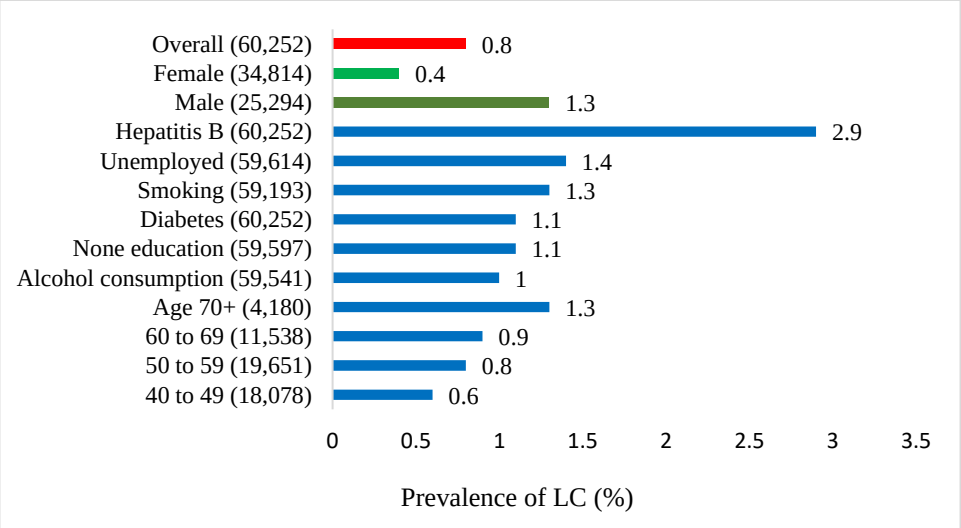

Figure 2 Prevalence of LC

Table 2 Prevalence of liver cirrhosis (LC), odds ratios (ORs) and 95% confidence intervals (Cis) from a simple logistic regression.

Factors	Number	%LC	Crude OR	95% CI	p-value
Gender					<0.001
Male	25,294	1.3	1		
Female	34,814	0.4	0.30	0.25 to 0.37	
Age					<0.001
40 to 49	18,078	0.6	1		
50 to 59	19,651	0.8	1.29	1.00 to 1.66	
60 to 69	11,538	0.9	1.63	1.24 to 2.14	
70+	4,180	1.3	2.24	1.61 to 3.12	
Education					0.503
None	537	1.1	1		
Primary	44,163	0.8	0.73	0.32 to 1.65	
Secondary (M1-M6)	9,962	0.7	0.61	0.26 to 1.41	
Certificate	955	0.9	0.84	0.30 to 2.37	
Bachelor +	3,883	0.7	0.62	0.25 to 1.51	
Occupation					0.044
Unemployed	1,475	1.4	1		
Famer	47,258	0.8	0.52	0.34 to 0.82	
Labor	3,407	1.0	0.72	0.42 to 1.24	
Own business	1,828	0.7	0.50	0.24 to 0.99	
Government official	3,802	0.7	0.50	0.28 to 0.88	
Other	1,748	1.1	0.76	0.40 to 1.42	
Smoking					<0.001
No	45,274	0.6	1		
Yes	13,823	1.3	2.14	1.77 to 2.57	
Alcohol consumption					<0.001
No	32,423	0.6	1		
Yes	27,021	1	1.78	1.48 to 2.15	
Hepatitis B					<0.001
No	58,871	0.8	1		
Yes	1,237	2.9	3.97	2.81 to 6.60	
Hepatitis C					<0.001
No	60,005	0.8	1		

Table 2 Prevalence of liver cirrhosis (LC), odds ratios (ORs) and 95% confidence intervals (Cis) from a simple logistic regression. (Cont.)

Factors	Number	%LC	Crude OR	95% CI	p-value
Yes	103	4.9	6.43	2.60 to 15.88	
Diabetes mellitus					0.069
No	57,159	0.8	1		
Yes	2,949	1.1	1.40	0.97 to 2.00	

To further clarify the association between gender and LC, a multiple logistic regression adjusted for the significant factors from the simple logistic regression (i.e. age, alcohol consumption, HBV, and DM) was performed. The rate of men who consumed and did not consume alcohol were nearly equal (1.3% and 1.4%, respectively). However, the rate of women who consumed alcohol was slightly greater than those who did not consume (0.6% and 0.4%, respectively). Our data presents an association between gender and LC based on alcohol consumption: women who do not consume alcohol have a lower risk of LC than men by less than 76% (OR = 0.24; 95% CI: 0.18 to 0.33; p-value <0.001). Conversely, women who do consume alcohol have a relatively lower risk of LC than men by less than 50% (OR = 0.50; 95% CI: 0.35 to 0.69; p-value <0.001). Therefore, women who drink alcohol present a stronger association to LC than those who do not drink alcohol (Table 3).

Table 3 Multivariable analysis presented by adjusted odds ratios and 95% confidence intervals (CIs)

Factor	Number	%LC	Crude OR	Adjusted OR	95% CI	p-value
Gender and LC according to drinking alcohol						
Never drink alcohol						<0.001
Male	7,237	1.4	1	1		
Female	25,186	0.4	0.25	0.24	0.18 to 0.33	
Have drank alcohol						<0.001
Male	17,786	1.3	1	1		
Female	9,235	0.6	0.45	0.49	0.35 to 0.68	
Gender and LC according to hepatitis B						
Hepatitis B negative						<0.001
Male	24,641	1.3	1	1		
Female	34,230	0.4	0.31	0.24	0.18 to 0.33	
Hepatitis B Positive						0.005
Male	653	4.1	1	1		

Table 3 Multivariable analysis presented by adjusted odds ratios and 95% confidence intervals (CIs) (Cont.)

Factor	Number	%LC	Crude OR	Adjusted OR	95% CI	p-value
Female	584	1.5	0.36	0.29	0.12 to 0.69	
Age						<0.001
40 to 49	18,121	0.6	1	1		
50 to 59	19,678	0.8	1.29	1.20	0.93 to 1.55	
60 to 69	11,548	0.9	1.63	1.46	1.10 to 1.92	
70+	4,185	1.3	2.24	1.98	1.41 to 2.78	
Diabetes mellitus						<0.001
No	57,300	0.8	1	1		
Yes	2952	1.1	1.65	1.55	1.06 to 2.28	

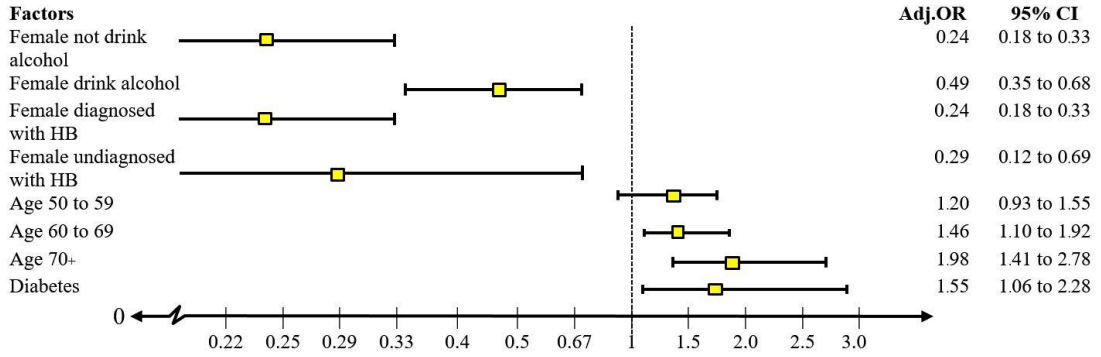

Figure 3 Factors associated with liver cirrhosis (LC) presented by adjusted ORs (Adj. OR) and 95% confidence intervals (CIs)

Discussion

Key findings

The principal finding from our study was identifying alcohol consumption as the main factor associated to liver cirrhosis in men and women. Women who consume alcohol have a relatively higher risk of LC compared to men who consume alcohol (OR = 0.50; 95% CI: 0.35 to 0.69; p-value <0.001). This is the first study to estimate the prevalence and investigate potential risk factors associated with gender differences in LC based on ultrasonography screenings in Northeast Thailand.

Strengths and weaknesses

Our study included certain limitations. The demographic information derived from interviewing subjects were obtained through a health questionnaire, which may have brought about a reporting bias. Alcoholism, HBV and DM were not confirmed by official medical diagnoses. However, this should have had minimal effect on our analysis since most of the medical conditions assessed in our analysis were chronic diseases that require long-term treatment. The major strengths of our study are that all data was taken from the large volume of CCA ultrasonography screened

patients enrolled in CASCAP. And CASCAP is a population-based ongoing cohort study being conducted across Northeast Thailand. This ensures that the results were generated and not greatly affected by temporality, which is commonly associated with cross-sectional studies.

Prevalence of liver cirrhosis (Strengths and weaknesses related to previous studies)

The overall prevalence of LC from our study was 0.8% from a study population of 60,108 subjects. Our reported prevalence was similar to a population-based case control study performed in the United States that reported LC in 0.27% from 29,906 subjects (Scaglione et al., 2015). As well as a prospective study conducted in France that reported a 0.3% prevalence from 7,463 subjects (T. Poynard et al., 2010; Scaglione et al., 2015).

The prevalence of LC in men was higher than women, 1.3% and 0.4%, respectively. The prevalence of LC increases with age and peaks in the >70 age group (1.3%). This is similar to the study conducted in the United States that reported the prevalence of cirrhosis steadily increasing with age and peaking in the 45-54 and >75 age group (Scaglione et al., 2015).

Logistic regression (Strengths and weaknesses related to previous studies)

Women who do not drink have a less than 76% association with LC (OR = 0.24; 95% CI: 0.18 to 0.33; p-value <0.001). Conversely, women who drink alcohol had a less than 50% association to LC (OR = 0.50; 95% CI: 0.35 to 0.69; p-value <0.001). Our results were similar to a study conducted in Japan that reported women were at risk for alcoholic-LC (Horie et al., 2013). As well as a study from Italy that found that women demonstrated a strong association with liver decompensation (type of LC) (Adjusted OR = 2.09; 95% CI: 1.10 to 3.97)(Romeo et al., 2009). The United States study illustrated a strong association between men and LC (adjusted OR = 2.44; 95% CI: 1.43 to 4.16; p-value <0.001)(Scaglione et al., 2015). In contrast to our study that report increased risk of LC in women and those in younger age groups, studies conducted in Taiwan report an increased risk among men and elderly populations (Huo et al., 2000)

Meaning and interpretation

Our study demonstrated an association between gender with LC; men are at greater risk of LC than women. The risk effect of LC may be related to fibrosis progression, ageing, and the presence of other risk factors. The effect of age on fibrosis progression for men aged 61 to 70 years old is more rapid than those aged 21 to 40 years old (Deuffic, Buffat, Poynard, & Valleron, 1999; M. d. T. a. T. Poynard, 2003). Based on previous studies regarding HBV and HCV, there is an increasing potential of fibrosis progression in men whereas, women had a higher association to the rapid progression of alcohol-induced LC, independent of age (M. d. T. a. T. Poynard, 2003; T. Poynard et al., 2003). Recently, evidence regarding the protective effect of estrogen via the inhibition of stellate cell proliferation, have demonstrated an association between female pregnancy, oral contraceptives and menopause with slow fibrogenesis (M. d. T. a. T. Poynard, 2003). Previous studies have also suggested the further evaluation of sex hormones that may lead to chronic liver diseases such as, LC (Durazzo et al., 2014).

Our results show that an increasing age increases the chance of LC, which is similar to the United States study showing increasing age increased risk of LC (Adjusted OR = 1.02; 95% CI: 1003 to 1.04; p-value: 0.020) (Scaglione et al., 2015). Our study discovered the following other factors associated with LC: subjects who consumed

alcohol, HBV and DM. Our results are consistent with the study in the USA that also found DM to be associated with LC (Adjusted OR = 2.59; 95% CI: 1.40 to 4.78; p-value: 0.002) (Scaglione et al., 2015). In addition, a New Zealand study found that DM and poor diabetic control was associated with the increasing rate of LC complications. DM can play a role in LC progression (Hsiang, Gane, Bai, & Gerred, 2015; Huo et al., 2000; Scaglione et al., 2015).

Future suggestions

The findings from this study may not be clear on gender with alcohol consumption because the question from the questionnaire did not specify the degree of drinking. The relationship does not very prominent even though the difference between men and women with alcohol consumption has been absolutely significant, a result from there were very large sample in this study. Therefore, the standards of setting an appropriate question in health questionnaires are very important in further study. If any studies have found the clear association between gender with alcohol consumption and liver cirrhosis, planning of disease prevention will play an important role greatly. Specifically, primary and secondary prevention, which can lead to sustained solving these health problems further.

Conclusions

In conclusion, women who consume alcohol have a greater association with LC than women who do not consume alcohol. Our findings can contribute to public health efforts aimed at controlling the burden of LC. Furthermore, we suggest targeting young women for early screenings of liver diseases such as LC. Future programs should incorporate educational programs regarding the harms of drinking alcohol, painting a clear picture of understanding the relationship of alcohol and cirrhosis with culturally-sensitive-practical ways to protect themselves from alcoholism and alcohol-centered environments or social gatherings. The ultimate and worthy aim including the prevention and reduction of CCA incidence in the new generation in Northeast Thailand.

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