Prevalence of Suspected Cholangiocarcinoma Based on Ultrasonography Screening and its Associated Factors in Northeastern Thailand

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ABSTRACT

Background

Ultrasonography of the liver allows detection of liver mass and bile duct dilatation which are findings of suspected Cholangiocarcinoma so that early stage Cholangiocarcinoma can be detected.

Objective

To estimate the prevalence of suspected Cholangiocarcinoma as well as its associated factors.

Method

These reported results were obtained from the baseline screening for Cholangiocarcinoma as of July 2013 of an ongoing project the Cholangiocarcinoma Screening and Care Program conducted in Northeastern Thailand. Participants were northeasterners who were at least one of the followings: 40 years or older, ever been infected with liver fluke, ever been treated with praziquantel, or ever been consumed raw fresh water fish. Ultrasonography was done by well-trained medical radiologists.

Result

Of the total 1,196,685 participants, 58.9% were females with a mean age of 58.2 (standard deviation ± 9.9) years. Suspected Cholangiocarcinoma was found in 15,186 (2.6%; 95% CI: 2.56 to 2.65) individuals. The results observed that the participants with higher age group had high association as compared to younger age group (AOR=1.98; 95% CI: 1.77 to 2.21; p-value < 0.001), hepatitis B infected participants were highly significant as compared to the non- hepatitis B infected (AOR=1.22; 95% CI: 1.07 to 1.39; p-value = 0.002) and participants having Hepatitis C were also significantly associated with Cholangiocarcinoma infection (AOR=1.46; 95% CI: 1.04 to 2.05; p-value = 0.029) based on ultra-sonographic screening respectively. However, patients having diabetes were less likely to be associated with Cholangiocarcinoma (AOR=0.87; 95% CI: 0.81 to 0.93; p-value ≤ 0.001).

Conclusion

About one out of a hundred cases required further investigations such as Magnetic resonance imaging or Computed Tomography. Early age of ultrasonography screening for Cholangiocarcinoma enhanced the opportunities for early detection of Cholangiocarcinoma and might reduce irrational requests for expensive or invasive methods of diagnosis.

KEY WORDS

Cholangiocarcinoma, Suspected case, Ultrasonography screening

INTRODUCTION

Ultrasonography of the liver allows detection of liver mass and bile duct dilatation, which are findings of suspected Cholangiocarcinoma (CCA) so that early stage CCA can be detected.[1,2] These suspected cases require high cost confirmatory diagnosis methods. Such ultrasound screening might lead to a high rate of MRI and CT scan prescriptions unnecessarily.[3,4]

Cholangiocarcinoma is a leading health concern in Thailand, especially in the Northeast region.[5-7] The prevalence of the disease is high and the incident rate has been reported the highest in the world with 113.4 and 49.8 per 100,000 populations in male and female respectively.[8-11] It is estimated that 20,000 new cases occur in a year.[12] Recently, there is no existing clinical practical guideline which is wildly accepted, causing unsatisfactory treatment outcomes.[13-15] Moreover, knowledge and understanding on diagnosis and treatment guideline among medical personnel is still lacking.[6,16,17] Most of them believe that the disease cannot be completely cured and the patients will finally end up with death despite receiving medical treatment.[18,19] It causes loss of opportunities for appropriate treatment and leads the patients to suffer before their death. Besides, there is no effective disease screening system, making it difficult to detect the patients with early stages of the disease.[20-23] Therefore, it is necessary to have a screening plan for the high risk group, systemic diagnosis and treatment for optimum outcomes and curative treatment as well as appropriate palliative treatment in order to improve quality of life.[24,25] This is also an initiative project, which can contribute to the changes in national public health policy in the future. Therefore, this study was aimed to estimate the prevalence of suspected CCA as well as its associated factors in Northeastern Thailand. So, the finding of this study will help to the program planner to introduce CCA screening program by ultrasonologically rather than diagnosis by MRI and CT. Which will reduce the diagnosis cost of CCA in an effective manner.

METHODS

This reported results from the baseline screening for CCA as of July 2013 of an ongoing project-the Cholangiocarcinoma Screening and Care Program (CASCAP), see details at www.cascap.in.th).[8,26] Northeastern Thailand has long been known to be the region with the world's highest rate of Cholangiocarcinoma. Northeasterners participants who were within at least one of the following criteria: 40 years or above, ever been infected with liver fluke, ever been treated with praziquantel, or ever consumed raw fresh water fish were recruited on this study. Ultrasonography was done by well-trained medical radiologists.

Suspected CCA was defined as individual who had either liver mass or bile duct dilatation based on the ultrasonography findings of the liver.

This study was conducted according to the International Conference of Harmonization (ICH) Good Clinical Practice (GCP) guideline and the Declaration of Helsinki. The final study protocol and the final version of the Written Informed Consent had been approved by Khon Kaen University Ethic Committee (HE551404).

Baseline characteristics of the participants were examined using descriptive statistics. Prevalence and its 95% confidence intervals (95% CI) of suspected CCA was estimated based on normal approximation to binomial distribution. The numerator was the number of participants whose ultrasonography findings was either liver mass or bile duct dilatation and the denominator was the total number of participants who were undergone ultrasonography. Magnitude of association between the suspected CCA and selected factors such as demographic and behavioral factors were estimated as odds ratios (OR) together with their 95% CIs by using multiple logistic regression analysis. All statistical analysis was performed two-sided tests with a significant level of 0.05. No adjustment of alpha level was made for multiple testing. All statistical analyses were implemented by using STATA 13 (Stata Corp, College Station, TX).

RESULTS

Out of 1,197,045 participants, the overall prevalence of suspected CCA was 2.61%. Suspected CCA was found in 4.33% of Unemployed participants, which was highest prevalence in this study. The prevalence of suspected CCA in male was higher than female (3.01% and 2.36%, respectively). In addition, this study also observed increase in the prevalence when the age is raised. Meanwhile, the study also observed higher education levels is associated with high prevalence as well. For all details of prevalence of suspected CCA, information is presented in table 1.

Table 1. Prevalence of suspected Cholangiocarcinoma

Factors	Total number	Number Suspected CCA	CCA (%)	(95%CI)
Overall prevalence	582,844	15,186	2.61	(2.56 to 2.65)
Gender				
Male	219,265	6,607	3.01	(2.94 to 3.09)
Female	363,426	8,576	2.36	(2.31 to 2.41)
Age				
40 to 44	23,310	378	1.62	(1.46 to 1.79)
45 to 49	79,894	1,379	1.73	(1.64 to 1.82)
50 to 54	110,328	2,153	1.95	(1.87 to 2.03)
55 to 59	22,011	588	2.67	(2.46 to 2.89)
Greater than 60	347,301	10,688	3.08	(3.02 to 3.14)
Education				
No formal education	10,694	378	3.53	(3.19 to 3.90)

Primary school	429,117	11,242	2.62	(2.57 to 2.67)
Secondary school (M1-M3)	52,367	1,182	2.26	(2.13 to 2.39)
Secondary school (M4-M6)	59,996	1,410	2.35	(2.23 to 2.47)
Certificate	8,062	249	3.09	(2.72 to 3.49)
Bachelor	17,541	562	3.20	(2.95 to 3.48)
Higher than Bachelor	4,206	135	3.21	(2.70 to 3.79)
Occupation				
Unemployed	25,740	1,115	4.33	(4.09 to 4.59)
Farmer	456,088	10,900	2.39	(2.35 to 2.43)
Labor	46,576	1,393	2.99	(2.84 to 3.15)
Own business	18,855	534	2.83	(2.60 to 3.08)
Government/State enterprise	18,817	617	3.28	(3.03 to 3.54)
Others	15,947	599	3.76	(3.47 to 4.06)
Ever had a stool examination for liver fluke infection				
Never	312,952	7,950	2.54	(2.49 to 2.60)
One	176,562	4,543	2.57	(2.50 to 2.65)
Two	51,306	1,366	2.66	(2.52 to 2.81)
Three	16,009	480	3.00	(2.74 to 3.27)
More than three	15,017	488	3.25	(2.97 to 3.55)
Can't remember	10,017	329	3.28	(2.94 to 3.65)
Ever been found to be infected by liver fluke				
Never been tested	313,918	7,972	2.54	(2.48 to 2.60)
Tested and found to be positive	87,777	2,511	2.86	(2.75 to 2.97)
Tested and found to be negative	165,274	4,263	2.58	(2.50 to 2.66)
Cannot remember	14,566	406	2.79	(2.53 to 3.07)
Ever been treated for liver fluke infection				
Never been treated	419,192	10,748	2.56	(2.52 to 2.61)
1 occasion	111,262	2,864	2.57	(2.48 to 2.67)
2 occasions	23,743	657	2.77	(2.56 to 2.98)
3 occasions	7,044	203	2.88	(2.50 to 3.30)
More than 3 occasions	8,564	319	3.72	(3.33 to 4.15)
Cannot remember	12,046	364	3.02	(2.72 to 3.34)
Family Members				
Uncle/Aunt (Younger)	5,308	150	2.83	(2.40 to 3.31)
Parents	56,492	1,328	2.35	(2.22 to 2.48)
Son/Daughter	833	36	4.32	(3.04 to 5.93)
Sibling	16,361	584	3.57	(3.29 to 3.87)
Nephew/Niece	451	17	3.77	(2.21 to 5.70)
Spouse	3,147	87	2.76	(2.22 to 3.40)
Smoking	117,989	4,204	3.56	(3.46 to 3.67)
Alcohol consumption	253,147	7,808	3.08	(3.02 to 3.15)
Alcoholic toxicity	8,148	255	3.13	(2.76 to 3.53)
Ever eaten uncooked or fermented fish	519,755	13,724	2.64	(2.60 to 2.68)
Underlying diseases				
Hepatitis B	8,794	284	3.23	(2.87 to 3.62)
Hepatitis C	1,011	40	3.96	(2.84 to 5.35)
Diabetes	40,870	1,045	2.56	(2.41 to 2.71)

Our bivariate analysis illustrated that the participants with higher age were more associated with CCA than the younger (OR = 1.93; 95% CI: 1.74 to 2.14; p-value < 0.001). The second highest association was among the persons whose relatives are suffering from Cholangiocarcinoma. Among family members, offspring such as son and daughter were highly associated as compared to the other family members (OR = 1.66; 95% CI: 1.19 to 2.32; p-value 0.006). Moreover, the study also observed cigarette smokers have 1.53 times more association than that of non-smokers (95% CI: 1.47% to 1.58% and p-value < 0.001) table 2.

Table 2. Effects of selected factors on suspected Cholangiocarcinoma

Factors	Suspected CCA		Suspected CCA		p-value
	Number	(%)	OR	95%CI	
Gender			**0.91**	**0.88 to 0.94**	**<0.001**
Male	219,265	3.01	1		
Female	363,426	2.36	0.78	0.75 to 0.80	
Age			**1.22**	**1.20 to 1.23**	**<0.001**
40 to 44	23,310	1.62	1		
45 to 49	79,894	1.73	1.07	0.95 to 1.20	
50 to 54	110,328	1.95	1.21	1.08 to 1.35	
55 to 59	22,011	2.67	1.67	1.46 to 1.90	
Greater than 60	347,301	3.08	1.93	1.74 to 2.14	
Education			**1.07**	**1.05 to 1.08**	**<0.001**
No formal education	10,694	3.53	1		
Primary school	429,117	2.62	0.73	0.66 to 0.81	
Secondary school (M1-M3)	52,367	2.26	0.63	0.56 to 0.71	
Secondary school (M4-M6)	59,996	2.35	0.66	0.59 to 0.74	
Certificate	8,062	3.09	0.87	0.74 to 1.02	
Bachelor	17,541	3.20	0.90	0.79 to 1.03	
Higher than Bachelor	4,206	3.21	0.91	0.74 to 1.11	
Occupation			**1.10**	**1.08 to 1.12**	**<0.001**
Unemployed	25,740	4.33	1		
Farmer	456,088	2.39	0.54	0.51 to 0.58	
Labor	46,576	2.99	0.68	0.63 to 0.74	
Own business	18,855	2.83	0.64	0.58 to 0.71	
Government/State enterprise	18,817	3.28	0.75	0.68 to 0.83	
Others	15,947	3.76	0.86	0.78 to 0.95	
Ever had a stool examination for liver fluke infection			**1.19**	**1.18 to 1.21**	**<0.001**

Never	312,952	2.54	1		
One	176,562	2.57	1.01	0.98 to 1.05	
Two	51,306	2.66	1.05	0.99 to 1.11	
Three	16,009	3.00	1.19	1.08 to 1.30	
More than three	15,017	3.25	1.29	1.17 to 1.41	
Can't remember	10,017	3.28	1.30	1.16 to 1.46	
Ever been found to be infected by liver fluke			**1.33**	**1.29 to 1.35**	**<0.001**
Never been tested	313,918	2.54	1		
Tested and found to be positive	87,777	2.86	1.02	0.98 to 1.06	
Tested and found to be negative	165,274	2.58	1.13	1.08 to 1.18	
Cannot remember	14,566	2.79	1.10	0.99 to 1.22	
Ever been treated for liver fluke infection			**1.17**	**1.15 to 1.19**	**<0.001**
Never been treated	419,192	2.56	1		
1 occasion	111,262	2.57	1.00	0.96 to 1.05	
2 occasions	23,743	2.77	1.08	1.00 to 1.17	
3 occasions	7,044	2.88	1.13	0.98 to 1.30	
More than 3 occasions	8,564	3.72	1.47	1.31 to 1.65	
Cannot remember	12,046	3.02	1.18	1.06 to 1.32	
Uncle/Aunt (Younger)			**1.52**	**1.29 to 1.79**	**<0.001**
No	468,846	2.65	1		
Yes	5,308	2.83	1.07	0.91 to 1.25	
Parents			**1.33**	**1.25 to 1.40**	**<0.001**
No	431,219	2.67	1		
Yes	56,492	2.35	0.88	0.83 to 0.93	
Son/Daughter			**2.27**	**1.63 to 3.16**	**<0.001**
No	472,225	2.65	1		
Yes	833	4.32	1.66	1.19 to 2.32	
Sibling			**2.00**	**1.84 to 2.18**	**<0.001**
No	460,271	2.63	1		
Yes	16,361	3.57	1.37	1.30 to 1.49	
Nephew/Niece			**2.02**	**1.25 to 3.27**	**0.003**
No	472,502	2.65	1		
Yes	451	3.77	1.44	0.88 to 2.33	
Spouse			**1.48**	**1.19 to 1.84**	**0.0003**
No	470,391	2.65	1		
Yes	3,147	2.76	1.04	0.84 to 1.29	
Smoking			**1.57**	**1.52 to 1.63**	**<0.001**
No	463,300	2.36	1		
Yes, either current or previous	117,989	3.56	1.53	1.47 to 1.58	
Alcohol consumption			**1.63**	**1.58 to 1.68**	**<0.001**
No	328,671	2.24	1		
Yes, either current or previous	253,147	3.08	1.39	1.35 to 1.44	
Alcoholic toxicity			**1.28**	**1.13 to 1.45**	**0.0001**
No	571,400	2.60	1		
Yes, either current or previous	8,148	3.13	1.21	1.07 to 1.37	
Ever eaten uncooked or fermented fish (specifically, fresh water with scales)			**1.87**	**1.77 to 1.98**	**<0.001**
No	62,140	2.29	1		
Yes, either current or previous	519,755	2.64	1.16	1.10 to 1.22	
Underlying diseases					
Hepatitis B			**1.68**	**1.49 to 1.89**	**<0.001**
No	465,305	2.65	1		
Yes	8,794	3.23	1.22	1.09 to 1.38	
Hepatitis C			**1.93**	**1.41 to 2.65**	**<0.001**
No	471,647	2.66	1		
Yes	1,011	3.96	1.51	1.10 to 2.07	
Diabetes			**1.05**	**0.98 to 1.11**	**0.1755**
No	435,961	2.67	1		
Yes	40,870	2.56	0.96	0.90 to 1.02	

In the multivariate analysis, we observed that the participants with higher age group have high association as compared with younger age group (adjusted OR = 1.98; 95% CI: 1.77 to 2.21; p-value < 0.001). HCV infected participants are second highly significant as compared with the non-HCV infected adjusted OR = 1.46; 95% CI: 1.04 to 2.05; p-value =0.029). The other factors remained significant, although Diabetes patients switched to a positive association. For all details of association of suspected CCA information is described in table 3.

DISCUSSION

This study purposed to examine and empirically tested the relationships between demographic information, ultrasound and confirmatory diagnosis. In addition, factors for early diagnosis of CCA among registered patients (CASCAP) in the Northeast of Thailand were investigated and addressed the associated factors for early screening of Cholangiocarcinoma (CCA) among Thai population in Northeast, Thailand. Our study revealed the participants with higher age group have high association as compared with younger age group. This finding is also matched with another study which has been conducted in Thailand that shows the majority of the respondents were from age group of 40-100 having CCA. This might be due to the increasing in age lead to the low immunity towards CCA.

In addition, Hepatitis B infected participants were second highly significant as compared with the non- HBsAg infected and participants having Hepatitis C were also significantly

Table 3. Multivariable analysis of factors affecting suspected Cholangiocarcinoma

Factors	Suspected CCA		Adj. Odds ratio	(95%CI)	p-value
	Number	(%)			
Age					
40 to 44	23,310	1.62	1		
45 to 49	79,894	1.73	1.10	0.98 to 1.25	0.118
50 to 54	110,328	1.95	1.24	1.10 to 1.39	<0.001
55 to 59	22,011	2.67	1.80	1.57 to 2.07	<0.001
Greater than 60	347,301	3.08	1.98	1.77 to 2.21	<0.001
Occupation					
Unemployed	25,740	4.33	1		
Farmer	456,088	2.39	0.58	0.54 to 0.62	<0.001
Labor	46,576	2.99	0.73	0.67 to 0.80	<0.001
Own business	18,855	2.83	0.69	0.62 to 0.78	<0.001
Government/ State enterprise	18,817	3.28	0.84	0.75 to 0.94	0.002
Others	15,947	3.76	0.87	0.78 to 0.97	0.016
Smoking					
No	463,300	2.36	1		
Yes, either current or previous	117,989	3.56	1.30	1.24 to 1.36	<0.001
Alcohol consumption					
No	328,671	2.24	1		
Yes, either current or previous	253,147	3.08	1.28	1.22 to 1.33	<0.001
Ever eaten uncooked or fermented fish (specifically, fresh water with scales)					
No	62,140	2.29	1		
Yes, either current or previous	519,755	2.64	1.12	1.05 to 1.19	<0.001
Underlying diseases					
Hepatitis B					
No	465,305	2.65	1		
Yes	8,794	3.23	1.22	1.07 to 1.39	0.002
Hepatitis C					
No	471,647	2.66	1		
Yes	1,011	3.96	1.46	1.04 to 2.05	0.029
Diabetes					
No	435,961	2.67	1		
Yes	40,870	2.56	0.87	0.81 to 0.93	<0.001

associated with CCA infection. The study conducted in Northeast Thailand in 2010 examined the association of HBsAg and HCV with CCA and reported a greater risk of CCA for those carrying the virus (OR=4, 95% CI 1.29 to16.44, $p < 0.05$).[24] However, another study conducted in similar region revealed that the positive diagnosis of HBsAg and HCV remained non-significant.[10] Furthermore, study in 2012 found that HBsAg and HCV were not related to CCA.[4] The region behind development of CCA has been acquired by the established mechanistic events for Hepatitis B or C viruses which consist of inflammation, liver cirrhosis, chronic hepatitis, and liver fibrosis.[27] However, patient having diabetes were less likely to be associated with CCA (AOR=0.87; 95% CI: 0.81 to 0.93; p-value ≤ 0.001).

As, this study was conducted on a large population across Northeast Thailand with a variety of cultural, well-being and environmental factors which significantly shows the strength. This can be a good representation of the population of Northeast Thailand as a whole, which will be able to study and used as references.

However, these study findings have identified factors that were associated with early screening of CCA in a high-risk population for CCA. Despite the problem the demographic data were derived from subject questionnaires, which are potentially biased as a medical diagnosis was not confirmed for HBsAg, DM and HTN. However, the limitations of data in this study, based on a very large sample size i.e. 48, strongly suggest that ultrasound has an important role for diagnosis of CCA. Moreover, the findings of this study also strongly suggest that ultrasound is highly significantly associated with CCA findings. Although, earlier studies have found evidence for a relationship between HBsAg and BDD not much; however, the relationship formed between HBsAg with BDD cannot be ignored.

Early detection of CCA by routine screening provides way to reduce the incidences of CCA. Thus, for surveillance, to minimize the risk of CCA, frequency of screening should be increased. To confirm CCA in the coming day's frequency of ultrasonic investigations should be increased.

Finally, limitation in this study is that the demographic information was derived from subject questionnaires. These are potentially biased as medical diagnosis was not confirmed for HBsAg, HCV, DM and HTN which could lead to an underestimate as some subjects may not be willing to disclose such results.

CONCLUSION

About one out of a hundred required further investigations such as MRI or CT scan. Ultrasonography screening for Cholangiocarcinoma provides an opportunity for early detection of CCA which might reduce irrationally requests for expensive or invasive methods of diagnosis.

Therefore, further study is necessary throughout the region to test the generality of our results. Nevertheless, these results can reflect the problem and solutions in a large sample cohort and can be used as a guideline in formulating clinical practice and future research priorities.

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