RESEARCH COMMUNICATION

Ultrasound Screening for *Opisthorchis viverrini*-associated Cholangiocarcinomas: Experience in an Endemic Area

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Abstract

In Thailand, liver cancer is the most common malignancy in males and the third most common among females. In the Northeast region, cholangiocarcinoma (CHCA) is the prevalent type, with Opisthorchis viverrini (OV), an endemic liver fluke, being considered the cause. We evaluated the role of ultrasound (U/S) for cholangiocarcinoma screening as part of a larger cohort to characterize the linkage between liver fluke infestation and CHCA in Khon Kaen (Northeast Thailand). Most people (77%) had normal U/S findings while only 0.5% had suspected CHCA; thus, U/S should be used primarily for those with the highest risk, presenting symptoms and/or being OV positive.

Key Words: Cholangiocarcinoma - liver cancer - *Opisthorchis viverrini* - ultrasound screening

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Introduction

Khon Kaen province is situated in Northeast Thailand and covers an area of 10,886 km^2 with a population of 1.73 million in 2000 (National Statistics Office, 2002). The liver fluke, *Opisthorchis viverrini*, is an important public health problem in the Northeast, because it is associated with a number of asymptomatic hepatobiliary abnormalities that can be observed by roentgenography and ultrasonography (U/S) (Dhiensiri et al., 1984; Elkins et al., 1990; Mairiang et al., 1992) and it is the putative etiology of CHCA (IARC, 1994), infecting an estimated 7 million people in total (Upatham et al., 1984; Preuksaraj, 1984).

Cohort studies are generally accepted as the most useful and valid type of investigation in observational epidemiology. The Khon Kaen cohort study was established as a community-based early detection and health education project. It was designed to improve the outcome of liver cancer. Details have been described previously (Sriamporn et al., 2005). U/S examination is relatively simple to perform and has a high level of community acceptance: U/S screening was therefore included in this project.

Subjects and Methods

The Khon Kaen University Ethics Committee reviewed and approved our research protocols.

Recruitment

Recruitment for the Khon Kaen cohort took place between 1990 and 2001. At the time of the study, Khon Kaen province had 20 districts, each comprising ~10 sub-districts. One or two sub-districts were randomly selected in each district, and recruitment started in all of the villages within it .

The eligible population was interviewed and examined during 2-3 weeks of field work, depending on the size of the resident population. Lists of the resident population were obtained and files of the eligible people were prepared. Each village was visited by the study team, with a mobile unit equipped with an U/S machine. Village residents had the examination and procedures explained to them as well the details of tests and examinations and the rationale for keeping part of the biological samples for retesting. Persons agreeing to participate signed the consent form.

All told, 25,000 subjects enrolled in the cohort. Since the number of radiologists was limited, U/S screening was performed only at recruitment. The number of subjects who received U/S screening was 4,154. The age and sex distributions of the subjects who underwent U/S screening are presented in Table 1.

Medical examination

The demographic and socio-economic characteristics of the participants were investigated through interviews. They

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Table 1. Age and Sex Distribution of Subjects who Underwent U/S Screening

Age group	Male		Female		Total	
	No	%	No	%	No	%
< 30	0	0	6	0.2	6	0.1
30-39	340	21.3	591	23.1	931	22.4
40-49	513	32.1	820	32.1	1333	32.1
50-59	400	25.0	661	25.9	1061	25.5
60-70	251	15.7	373	14.6	624	15.0
> 70	94	5.9	105	4.1	199	4.8
Total	1,598	100	2,556	100	4,154	100

Table 2. Diagnostic Criteria for Sonography

Status	Character
Normal gall bladder (GB): Sharp wall, no sludge	
Mild GB disease: Presence of sludge and poor wall definition	
Gall stones:	Presence of one or more stones
Chronic cholecystitis:	Gall bladder length > 8 cm. More than 4 standard deviations of uninfected people (Mairiang et al.,1992). Increased periportal echoes-prominence of echoes along the portal triad (Homeida et al., 1988)
Suspected cholangiocarcinoma: Observation of one or more of the following -a mass, -a dilated intrahepatic duct, or –a hydrop gall bladder	

then underwent a general physical examination and U/S examination of the abdomen. Blood pressure, height, weight were also measured and recorded.

Ultrasound examination

Abdominal sonography was performed after at least 6 hrs fasting. We used a full-size high-resolution machine (Hitachi model EUB 450, with a 3.5 MHz convex array probe). Radiologists who performed the sonography were not apprised of the parasitological status of any of the enrolled subjects.

The maximum gall bladder length was measured after locating the largest image in all planes. Abnormalities, such as the presence of sludge, poor definition of the wall, gall stone(s) and increased periportal echoes, were recorded. The sonographic criteria used in the diagnosis of hepatobiliary status are listed in Table 2. Diseases of other organs in the abdomen and pelvis, if detected, were also recorded. Renal stones were recorded separately because renal stone disease also has a high prevalence in this region and, as such, the data could be used for future community research.

Fecal specimens

The presence of OV eggs was assessed in feces using Stoll's semi-quantitative egg count.

Referrals and follow-up

Participants who were OV positive or had abnormal U/S findings were informed and advised to seek treatment. The suspected CHCA cases were invited for further investigation.The follow-up of suspected CHCA cases was carried out by linkage of the study database with the death registry for Khon Kaen Province and the Khon Kaen Population-based Cancer Registry (Sriamporn et al., 2005).

Results

We enrolled 4,154 subjects in the study, ranging between 22 and 92 years of age (mean, 49.3; SD, 11.2) (Table 1). Overall U/S findings are summarized in Table 3 and imaging details for one case are illustrated in Figure 1.

Results of follow-up of suspected CHCA cases

All suspected CHCA cases were invited for further investigation with computed tomography (CT) of the upper abdomen and/or endoscopic retrograde cholangio-pancreatography (ERCP). Only three subjects agreed to the investigation but they refused to undergo an operation. The remainder of the participants all refused either any further investigation or surgery.

After 14 years follow-up, 38% of the cases (8/21) were reported to have died from liver cancer, 5% (1/21) to have died from carcinoma of the cervix, 14% (3/21) to have died from cardiovascular disease, and 38% (8/21) to have survived.

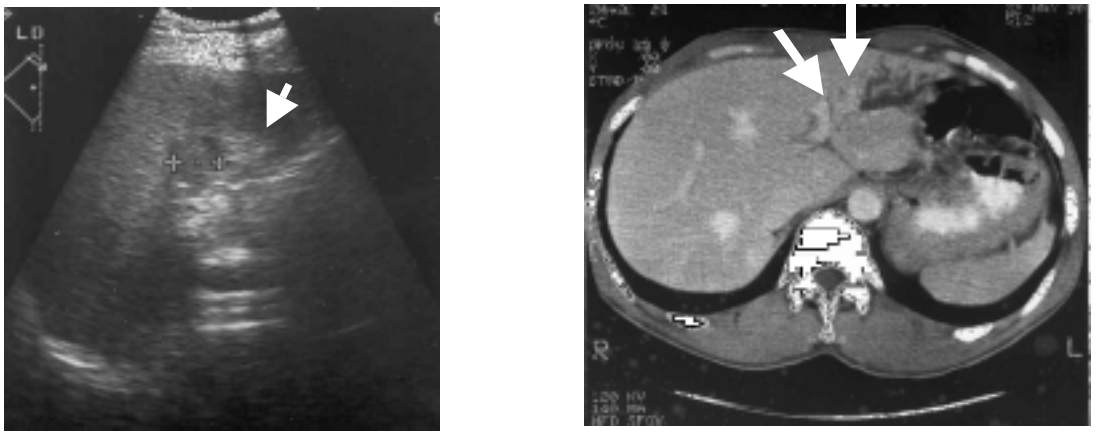

Figure 1. a) U/S of a Suspected CHCA Case Shows a Characteristic Mass in Segment 3 of the Liver (arrow). b) CT of the Same Subject Confirms the Mass and Dilated Intrahepatic Ducts (double arrows).

Table 3. Summary of the Results of U/S Screening

U/S finding	Male		Female		Total	
	No	%	No	%	No	%
Normal	1160	72.6	2052	80.3	3212	77.3
Mild GB	23	1.4	32	1.3	55	1.3
Gall stone	72	4.5	142	5.6	214	5.2
Chronic cholecystitis & increased periportal echoes						
	37	2.3	30	1.2	67	1.6
Suspected CHCA	11	0.7	10	0.4	21	0.5
Other liver diseases*	89	5.6	63	2.5	152	3.7
Disease of other organs, not renal stones						
	113	7.1	139	5.4	252	6.1
Renal stones	93	5.8	88	3.4	181	4.4
Total	1,598	100	2,556	100	4,154	100

*Including fatty liver, cirrhosis, simple cysts of the liver, and other benign liver masses according to U/S criteria

Discussion

Our present results indicate that while U/S can help diagnose CHCA and other hepatobiliary changes the prevalence in the general population is not sufficient to warrant the costs involved , especially given the refusal of patients to undergo further treatment. This is in fact a major finding of the present study.

Flukes are known to cause damage to liver cells, Kupffer cells, macrophages and within epitheloid and giant cells in egg granuloma (Sripa et al., 2000). Other studies show nucleic damage by reactive nitrogen and oxygen species in hamsters infected with OV (Pinlaor et al., 2003, 2004). These results support the role of OV as carcinogenesis-associated with chronic infection and inflammation.

There are 2 types of CHCA. The peripheral (intrahepatic) type and central (extrahepatic type) (Uttaravichien, 1989). Most patients with peripheral CHCA present with a palpable liver mass; the mass may be single or multiple and may involve one or both lobes of the liver. The most common presentation of the central CHCA is obstructive jaundice, which progresses gradually without fever until the late stage. This complex pathology makes U/S alone inadequate for the diagnosis of CHCA.

To conclude, U/S is too expensive and personnel-intensive to be cost effective for screening the general population; thus, it should be reserved for persons with hepatobiliary symptoms and/or positive for OV. Moreover, U/S alone is not sufficiently sensitive for total detection of CHCA; therefore, further investigation would be needed to confirm any diagnosis. Appropriate preventive measures for reducing the frequency of infection are necessary and would include: 1) educating people to cook fish; and 2) hygienic toilet behavior.

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