RISK FACTORS FOR AND PREVALENCE OF CLONORCHIASIS IN MIAOLI COUNTY, TAIWAN

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Abstract. The objective of this study was to investigate the risk factors for and prevalence of clonorchiasis in Miaoli County, Taiwan. In 2009, 6,929 subjects were randomly selected in Miaoli County and given a questionnaire to fill out regarding risk factors for clonorchiasis; the response rate was 69%. Stool sample was obtained from each participant who filled out the questionnaire and examined using the merthiolate-iodine-formaldehyde concentration (MIFC) technique to determine the presence and concentration of *Clonorchis sinensis* eggs. Fifty-one subjects gave a history of clonorchiasis (prevalence rate 0.7%). Seven stool samples were positive for *C. sinensis* (prevalence rate 0.1%). Shihtan Township (5.0%) in Miaoli County had the highest prevalence of clonorchiasis. Using logistic regression, we found people who often fished (OR: 3.65, p=0.013) or who had a family member with a history of clonorchiasis (OR: 18.7, p<0.001) were more likely to have it. We also found tourists who traveled to China and ate fish there (OR: 2.46, p=0.105) or who owned a fish pond (OR: 1.93, p=0.128) were more likely to get clonorchiasis. The prevalence of clonorchiasis in Miaoli County was relatively low, which can be explained by good sanitation and personal hygiene. The Public Health Department of Taiwan should warn Taiwanese travelers about high risk areas for contracting clonorchis infection and encourage these travelers to avoid going fishing or eating raw fish in high risk areas.

Keywords: clonorchiasis, prevalence, risk factors, freshwater fish, Taiwan

INTRODUCTION

Clonorchis sinensis is associated with liver cancer among people who live in China, Russia, Vietnam, and Korea (Rim, 2005; Choi *et al*, 2006; Dang *et al*, 2008). Clonorchiasis is associated with pyogenic cholangitis and cholangiocarcinoma (Choi *et al*, 2004). The life cycle of *C. sinensis* has been well documented (Rim, 1986; Guoqing *et al*, 2001). Fifty-six percent of 681 civil servants surveyed in Miaoli County, Taiwan had clonorchiasis (Ong and Lu, 1979). In the past, clonorchaisis was common in Taiwan (Ong and Lu, 1979; Chen, 1991). The prevalence of clonorchiasis among the residents of 18 townships in Miaoli County was 11.6% in one study (Chou *et al*, 1994). The main reason for this high infection rate in the

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past was contamination of ponds and lakes with sewage(Chen, 1991). Taiwanese like to eat raw freshwater fish soaked in vinegar or red-pepper as an appetizer at social gatherings. The consumption of raw fish increases the risk of contracting clonorchiasis.

Known hosts for *C. sinensis* are humans, dogs, pigs, cats, martens, badgers, mink, weasels and rats (Ong and Lu, 1979; Chen, 1991). *C. sinensis* eggs are deposited in the biliary trees of these mammalian hosts, enter their intestines, and are passed out in the feces (Ong and Lu, 1979). When *C. sinensis* eggs flow into a pond, they are ingested by snails. Within the snail, the eggs undergo metamorphosis and asexual reproduction for 4 to 5 weeks, after which time the cercariae grow and develop in the water (Rim, 1986). These free-swimming forms of *C. sinensis* penetrate the skin of freshwater fish. Humans and other fish-eating mammals then become infected with *C. sinensis* by consuming these raw or inadequately cooked fish. Adult *C. sinensis* reproduce in the biliary tract and intrahepatic bile ducts, causing the bile ducts to swell over time (Huang *et al*, 2005).

Previous studies (Ong and Lu, 1979; Chang *et al*, 1988; Chou *et al*, 1994) have shown that clonorchiasis is highly common in Miaoli County. As a consequence, the Taiwanese government has attempted to eliminate possible sources of *C. sinensis* by forbidding people from using sewage as fertilizer, by educating residents in Miaoli about not eating raw fish, and telling people who think they may have contracted *C. sinensis* to immediately seek medical attention (Chou *et al*, 1994). It is unclear how many people have recently been infected with *C. sinensis* in Miaoli. Taiwanese travelers may also contract clonorchiasis when they travel to other countries, then bring the parasite back home to Taiwan. Although clonorchiasis does not currently pose a serious public health problem in Taiwan, it is necessary to monitor the prevalence of clonorchiasis and understand the risk factors for contracting *C. sinensis* infection.

MATERIALS AND METHODS

Study population

A representative cohort was established based on proportion probability sampling (PPS); we randomly selected 10,000 residents (as a reference population in Miaoli County) aged >20 years from 5,700 families living in 18 townships in Miaoli County , Taiwan for determining the prevalence of clonorchiasis in 2009. The Institution Review Board (IRB) in Yang-Ming University reviewed and approved our proposal. Of these 10,000 residents, we interviewed the 6,929 subjects who comprised our study population; each participant gave written, informed consent.

Questionnaire

A questionannaire was developed by the researchers and a pilot study was conducted to improve the clarity, validity, and reliability of the questions by testing a pilot group first. Five experts evaluated the validity of the questionnaire, the content validity index (CVI) of the questionnaire was 94%. The test-retest reliability (Kappa value) was 0.81 to 0.90. Each participant filled out a questionnaire by answering questions regarding demographics (gender, age, how long they lived in their house, education level and marital status) and the risk factors for clonorchiasis, namely frequency of fishing, having a family member with a history of clonorchiasis, having gone fishing in China, having eaten fish in China,

Table 1
Factors associated with *C. sinensis* infection using multiple logistic regression analysis.

	Odds ratio (95%)	*p*-value
Gender		
Female	1	
Male	7.14 (3.17-15.6)	<0.001
Frequency of fishing		
Seldom	1	
Occasional	3.55 (1.84-6.86)	<0.001
Often	3.65 (1.30-9.68)	0.013
Do you own a fish pond?		
No	1	
Yes	1.93 (0.83-4.48)	0.128
Have you eaten freshwater fish in China during the past year?		
No	1	
Yes	2.46 (0.83-7.27)	0.105
Family member who had clonorchiasis		
No	1	
Yes	18.7 (8.53-41.29)	<0.001

and living near a pond. The questionnaire also asked about non-specific symptoms of clonorchiasis (feeling uncomfortable, dizzy, experiencing swelling in the abdomen, feeling fatigued, experiencing pain in the joints, having headaches, having nausea or vomiting, having diarrhea and constipation and experiencing weight loss) during the previous three months.

Detection of *Clonorchis sinensis*

Fifty to 100 grams of stools were obtained from each subject. The specimens were examined using the merthiolate-iodine-formaldehyde concentration (MIFC) method according to standard operating procedures and *C. sinensis* eggs were quantitatively enumerated and expressed as eggs per gram of stool (epg). One gram of stool was mixed with 10 ml of MIF and a 5% iodine solution. The mixture was then shaken and poured into a bottle which contained several sieves (45 mm) to filter the mixture. Ether was added and the mixture was centrifuged for 2 minutes at 2,000*g*. A drop of the sediment was put on a slide, and examined under a microscope.

Statistical analysis

The data were analyzed using SPSS/PC 12.0 software, and the prevalence of clonorchiasis in the 18 townships in Miaoli was calculated. Logistic regression was used to find the people with the highest risk of contracting clonorchiasis. A *p*-value <0.05 was considered statistically significant.

RESULTS

Forty-eight percent of the participants in our study were male. Twenty-one percent of participants were aged 61-70 years, and 20% of them were aged 51-60 years. One fourth of the people in our study were high school graduates and 13% had

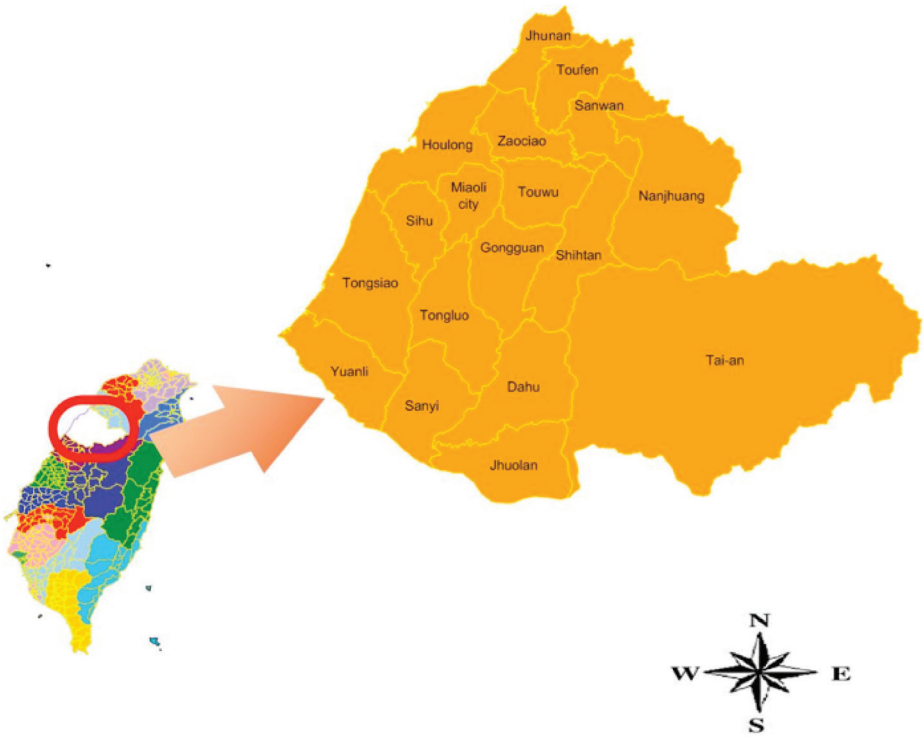

Fig 1–Map showing 18 townships in Miaoli, Taiwan.

received no formal education. Eighty-five percent of participants were married and 60% of the participants were Hakka (a minority group in Taiwan). Fig 1 shows a map of the 18 townships in Miaoli County, Taiwan. Fig 2 compares the prevalence of clonorchiasis in the 18 townships in Miaoli County between 1994 and 2009.

Multiple logistic regression analysis (Table 1) showed men were 7.1 times more likely than women to contract clonorchiasis. People who went fishing frequently were 3.7 times more likely to contract clonorchiasis than people who seldom went fishing. People with a family member who had contracted clonorchiasis were 18.7 times more likely to contract the infection than people who did not have a family member who had contracted clonorchiasis. Taiwanese tourists who had eaten freshwater fish in China during the previous year were 2.46 times more likely to contract clonorchiasis than those who had not eaten freshwater fish in China during the previous year; but this difference was not significant.

DISCUSSION

The World Health Organization (WHO) and International Agency for Research on Cancer in 1994 reported approximately 7 million people world-wide were infected with *C. sinensis* (IARC, 1994). However, Keiser and Vargas (2010) estimated 601 million people being at risk for contracting clonorchiasis and an estimated over 35 million people had chonorchiasis. In 1994 Chou *et al* reported the prevalence of clonorchiasis in Miaoli County, Taiwan was 11.6%. However, in 2009 only 0.1% of people surveyed in Mi-

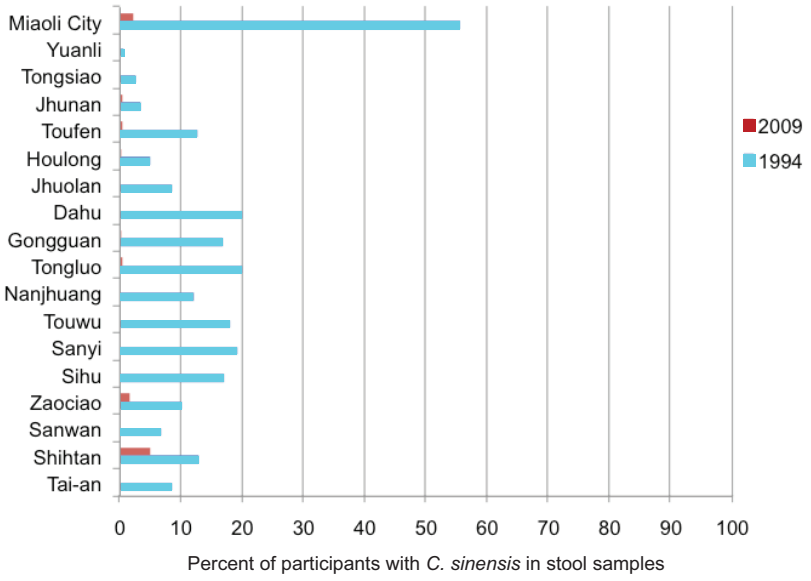

Fig 2–Percent positive stools for *C. sinensis* by location and date.

aoli County were infected with *C. sinensis*. In our study, 0.7% of subjects stated they had a history of clonorchiasis. Shihtan township had the highest prevalence of clonorchiasis (5.0%), which could be explained by the fact that this township is near the mountains and has many ponds. Most of the residents of Shihtan township are of a low socioeconomic status (Chou *et al*, 1994). In the past, septic tanks in Taiwan did not kill parasites; consequently, sewage containing *C. sinensis* was discharged into rivers or ponds. Human feces were used as fertilizer for vegetables or to breed freshwater fish in ponds. Therefore, C. *sinensis* spread easily in shellfish and reproduced in the freshwater supply. After 1994, physicians in Taiwan have been able to effectively treat clonorchiasis (Yen *et al*, 1993). Beginning in 2000, human feces were no longer used as a fertilizer in Taiwan. Septic tanks now kill most parasites; consequently, in 2009 the prevalence of clonorchis infection was low (Yeh *et al*, 2001).

In humans, clonorchiasis may be asymptomatic. However, chronic clonorchiasis is associated with hepatobiliary disease, such as biliary obstruction, recurrent pyogenic cholangitis (Lim, 1991), hepatolithiasis (Huang *et al*, 2005) and cholangiocarcinoma (Choi *et al*, 2006; Zhou *et al*, 2008).

In our study, people who felt dizzy (OR=1.84), had diarrhea (OR=3.11), constipation (OR=2.31) or had weight loss (OR=3.96) were more likely to have clonorchiasis. In our study, none of the subjects examined had obvious hepatobilitary disease and the questionnaire revealed no symptoms specific for clonorchiasis.

The pathologic and clinical consequences of clonorchiasis are related to density of infection, and host immunity. People with clonorchiasis are usually treated as outpatients. Wang *et al* (2006) found 41% of 282 subjects had clonorchiasis. Some studies may underestimate the prevalence of clonorchiasis. Stool samples have been used to screen for clonorchiasis. Although stool examinations and bile cytology for adult worms and/or eggs have a high specificity, the sensitivity is only10-12%, which results in underestimating the prevalence of clonorchiasis (Hong *et al*, 1998). Sometimes many people are unwilling to provide stool samples. Detection of serum antibodies to *C. sinensis* using ELISA or intradermal testing using diluted antigens of *C. sinensis* are the easiest tests

to perform, but they have a low specificity due to cross-reactivity with other parasites, such as *Paragonimus westermani* (Kim, 1998; Kim *et al*, 2010). Diffuse dilatation of intrahepatic bile ducts on transabdominal ultrasonography, abdominal CT and cholangiography have been used to diagnose hepatobiliary disease (Choi *et al*, 2004), but these methods also have a low specificity for diagnosing clonorchiasis. It is difficult to diagnose clonorchiasis only using radiological tests examining for intrahepatic bile duct dilatation.

Kim *et al* (2009) studied 3,080 patients in Korea who suffered from gastrointestinal diseases; 396 (12.9%) had clonorchiasis and 1,140 patients (37.2%) had a history of eating raw freshwater fish. Of those with a history of raw freshwater fish ingestion, 238 (20.9%) had clonorchiasis. The authors concluded clonorchiasis was common among patients with gastrointestinal disease in Korea, and the prevalence had not decreased much over the previous two decades. Yajima *et al* (2009) found that using a questionnaire to investigate the habit of eating raw, freshwater fish proved feasible in identifying individuals at high risk for contracting clonorchiasis.

Septic tanks in developing countries might not effectively kill parasites (Yen-Phi *et al*, 2010). Sewage, which might contain *C. sinensis,* may be used as fertilizer may be discharged into rivers and ponds. Clonorchiasis is often found among people who live near rivers and streams (Kim *et al*, 2002). People who live in southern Korea, where there are many rivers, have higher rates of clonorchiasis (17.3-40.2%) than people who live in central Korea where there are few rivers *(*8.0-17.3%) (Seo *et al*, 1981). This is consistent with our findings, indicating significant risk factors for clonorchiasis included fishing frequently and owning fish ponds. We also tested 95 fish and snail specimens, but did not find any infected with *C. sinensis* (data not shown). In Taiwan, fewer freshwater fish and snails are contracting *C. sinensis* because human feces are no longer used as fertilizer and septic tanks now kill most parasites (Cheng *et al,* 1990).We found a low prevalence of clonorchiasis in our study.

C. sinensis is common in China along streams and ponds and in freshwater fish (Yu *et al,* 2003; Zhang, 2007). Forty-two percent of men and 21% of women in one study from southern China had clonorchiasis (Zhang *et al*, 2007). Many cats and dogs have contracted clonorchiasis, then the local residents become infected with this parasite (Yu *et al*, 2003). A study from Shenzhen, a large city in southern China (Zhang *et al,* 2007), showed only 1.15% of snails were infected with the cercariae of *C. sinensis;* however, 41% of fish were infected with the metacercariae of *C. sinensis* because people use human and domestic animal feces to feed fish in ponds. Another study from China (Wang *et al*, 2006) found 26.4% of dogs had clonorchiasis. Lin *et al* (2005) found the *C. sinensis* infection rates in pigs, fish, dogs and cats in southern China were 27, 40, 50 and 70%, respectively. Our study found a significant relationship between having gone fishing in China, having eaten raw fish in China and contracting *C. sinensis* infection. Taiwanese who have been to other Asian countries and have hepatobiliary symptoms are more likely to be infected with *C. sinensis* (Fan *et al,* 2001). People with a history of clonorchiasis in our study complained of being easily fatigued (31%), dizziness (24%), constipation (22%) and diarrhea (20%). In one study, 17% of 1,758 aboriginal people infected with *C. sinensis* in Nantou, Taiwan, had similar symptoms (Yen *et al,* 1993).

Ninety percent of people we treated in Nantou using praziquantel at a dose of 25 mg/kg divided TID were cured within one year (Yen *et al*, 1993). Twenty-one percent of people we treated with praziquantel had side effects, including nausea, vomiting, dizziness and abdominal pain (Chen and Hsieh, 1982; Yen *et al*, 1993). The effect of drug combinations (praziquantel, artemether, artesunate, OZ78 and tribendimidine) against *C. sinensis* requires further scientific study (Yen *et al*, 1993; Fan *et al*, 2005).

A study from the United States (Stauffer *et al*, 2004) of 1,800 stool samples collected from 1,100 people over a 6-year period showed 1.3% of these people were infected with *Opisthorchis* spp or *C. sinensis*; the vast majority of those infected in that study were immigrants from Lao PDR, Cambodia and Thailand. Another study from northern Vietnam (Dang *et al*, 2008) found 26% of people examined had clonorchiasis, and the infection rate was 3.6 times higher among men than women. People who eat raw fish in Vietnam are 53 times more likely to contract clonorchiasis than people who do not eat raw fish (Dang *et al*, 2008). In order to eradicate clonorchiasis in Taiwan, the government screens immigrants and foreign workers from developing countries in Asia for clonorchiasis every six months (Fan *et al*, 2001). The Taiwanese government also collects stool samples from people who live in areas of Taiwan where there is a high concentration of *C. sinensis*, especially in remote and mountainous regions (Chen and Hsieh, 1982; Chang *et al*, 1988; Chou *et al*, 1994). Taiwanese who travel to China and have hepatobiliary symptoms are not being reported by physicians in Taiwan because some physicians are not familiar with clonorchiasis. The general population and physicians should be educated about clonorchiasis, including risk factors and control strategies. The Taiwanese government is currently taking steps to improve sanitation, periodically announcing areas at high risk for contracting clonorchiasis, promoting personal hygiene and recommending avoiding consumption of raw fish in high risk areas (Yeh *et al*, 2001).

In summary, in our study 51 subjects (0.7%) stated they had a history of clonorchiasis in the past. Seven subjects (0.1%) had stool samples positive for *C. sinensis*. The prevalence of *C. sinensis* infection among subjects in this study from Miaoli County, Taiwan was low. A main reason for this low prevalence could be that sewage is no longer dumped in ponds in Taiwan. People who often fish or travel to China and eat fish there were more likely to contract clonorchiasis. We recommend Taiwanese tourists who travel to other countries avoid eating raw or undercooked freshwater fish.

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