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Prevalence of *Opisthorchis viverrini* infection and incidence of cholangiocarcinoma in Khon Kaen, Northeast Thailand

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Summary Liver cancer is the most common cancer in Khon Kaen, Northeast Thailand, because of the high incidence of cholangiocarcinoma (CHCA). *Opisthorchis viverrini* (OV), a liver fluke, is endemic in the area, and has been evaluated as a cause of CHCA by International Agency for Research on Cancer. Residents of 20 districts in the province were invited to attend a mobile screening programme between 1990 and 2001. Of 24 723 participants, 18 393 aged 35–69 years were tested for OV infection, by examining stools for the presence of eggs. Prevalence of infection in each district was estimated from the sample of the population who had been tested. The incidence of liver cancer in 1990–2001 was obtained for each district from the cancer registry. The average crude prevalence of OV infection in the sample subjects was 24.5%, ranging from 2.1% to 70.8% in different districts. Truncated age-standardized incidence of CHCA at ages >35 years varied threefold between districts, from 93.8 to 317.6 per 100 000 person-years. After adjustment for age group, sex and period of sampling, there was a positive association between prevalence of OV infection and incidence of CHCA at the population level. Associations between CHCA and active OV infection in individuals have become hard to demonstrate, because of effective anti-OV treatment. The relationship may, however, be clear in comparisons between populations, which, for infectious diseases, take into account the contextual effects of group exposure in determining individual outcome. The cancer registry is an appropriate tool for disease monitoring in small areas.

keywords *Opisthorchis viverrini*, cholangiocarcinoma, liver cancer

Introduction

Khon Kaen province is situated in the north-eastern region of Thailand. It covers an area of 10 886 km^2 and had a population of 1.73 million in 2000 (National Statistics Office 2002). It has long been known as an area where infection with the liver fluke *Opisthorchis viverrini* (OV) is endemic, due to the habit of eating small raw fishes (koi pla) as a garnish for the local staple of sticky rice. The fish become infected with OV via a first intermediate host, a variety of *Bithynia* snails (Sadun 1955). A population-based cancer registry has been operating in the province since 1988, and data on all incident cases of cancer diagnosed since 1985 are included in its database (Vatanasapt *et al.* 1992). Results from the registry show that primary liver cancer incidence in Khon Kaen is very high, and in 1988–89 was the highest in the world with the age-standardized (world) incidence rate of 90.0 per 100 000 person-years in men and 38.3 per 100 000 person-years in women (Vatanasapt *et al.* 1992). Based on this observation, and other studies, the International Agency for Research on Cancer (IARC) (1994) declared OV to be a human carcinogen.

Despite the overall high risk of liver cancer, and specifically cholangiocarcinoma (CHCA), in OV-infected individuals, only a minority will develop cancer, and the incidence varies considerably by district within the province (Sriamporn *et al.* 1993). Partly in order to further investigate the role of OV and other co-factors in the genesis of liver cancer, the Khon Kaen Cohort Study was established in 1990. Initially, it was conceived as a community-based early detection and health education project, designed to improve the outcome of cancer and some other non-communicable diseases in the rural population of Khon Kaen, Northeast Thailand. Then in 1992, a collaborative project was established with IARC. This sought to formalize the recruitment, so that the epidemiology of major cancers could be studied. A faecal specimen was obtained from each of the cohort participants for detection of OV eggs. By April 2001, which was the end of the recruitment period, a total of 24 723 subjects had been enrolled, 16 652 women and 8071 men.

We report upon the association between infection with OV in the population recruited into the study from the different districts within the province, and the association with incidence of CHCA in the population of the same districts.

Materials and methods

Study cohort

During the phase of recruitment to the study cohort, villages in the province were selected for participation and the eligible population (35 years and older) recruited during 2–3 weeks of fieldwork. All 20 districts were included. Initially, one subdistrict was selected from each at random, and one of the villages within it chosen, based on the recommendation of the local health personnel (to maximize compliance). Later, for some districts, screening took place in all subdistricts; or, in other districts, all of the villages in the chosen subdistrict were screened. For some districts, more than one subdistrict was sampled. As a result, the sampling fraction by district was quite variable, and the time period during which the populations of different districts were tested was quite different.

During study recruitment, the head of the village was contacted and the aim of the intervention explained. Lists of the resident population were obtained and files of eligible people prepared. The study team visited the village, with a mobile unit equipped with an ultrasound machine. The unit was then installed in the village and the population invited to participate. Village residents willing to participate were informed of the examinations and procedures they would undergo and the rationale of keeping part of their biological samples for future research investigations was explained. Those who accepted to participate signed a consent form and were interviewed by trained staff. A sample of faeces was collected in a small plastic container and stored in an ice box for about 2–3 days before being transferred to the laboratory for examination.

Faecal samples were processed by the formalin ethyl acetate concentration technique (Elkins *et al.* 1990). When of OV eggs were found, the intensity of eggs per gramme (EPG) of faeces was determined by using Stoll's egg count.

Exposure data

The records of 18 393 individuals aged 35–69 years, who had been tested for OV eggs were included in the analysis. District of residence was coded according to the district boundaries (20 districts) at the beginning of the study (1990). In 1994, local government reorganization increased the number of districts to 25, but for the purposes of this study, the original 20 were retained. Four age groups were created: 35–44, 45–54, 55–64 and 65–69. The enrolment period was split into two 6-year periods: period 1 (1990–1995) and period 2 (1996–2001).

Registry data

During the same period (1990–2001), 5748 cases of primary liver cancer were recorded in the Khon Kaen cancer registry, among the population of all districts. Fifty-one cases of hepatocellular carcinoma (HCC; morphology code = 8170) were excluded from the analysis, as were 13 cases of unknown age. The remaining cases are referred to as CHCA; they were grouped into the same four age groups (35–44, 45–54, 55–64 and 65–69), and time periods of diagnosis (1990–1995 and 1996–2001).

Population data

The population denominators used were taken from the population censuses of 1990 and 2000 (National Statistics Office 1994, 2002). The sex-, age- and district-specific populations in these 2 years were linearly interpolated to obtain population estimates for each year throughout the period. Person-years of observation for periods 1 and 2, grouped by the same four age intervals as the cohort, were computed as the sum of populations estimated each year.

Data analysis

The incidence of CHCA was summarized by age-standardized rates, using the same weight for each age group, truncated to age 35 years and above.

The prevalence of OV-infected individuals in each district was adjusted for the age, sex and period distribution of the district population. The logarithm transformation was applied to the age-, sex- and period-specific proportions of infected individuals in the cohort to compute district averages and their confidence intervals (CI), weighted by the district age- and sex-specific population (Snedecor & Cochran 1980). The association between the incidence of CHCA and the prevalence of OV-infected population in each district was studied first by plotting the age-, sex- and period-adjusted mean prevalence of OV against incidence of CHCA in a scattergram and estimating the correlation coefficient (Pearson).

Then, a Poisson model was fitted to the data, with the number of incident cases (by sex, age, time period and district) as a function of number of infected individuals, with age group, sex and time period as covariates, the number of subjects tested as weight, and the population at risk as offset. This analysis was repeated with counts of infected individuals including only those with high concentrations of eggs in stool. Cut-off points adopted were 600, 1500 and 6000 EPG.

Results

The overall crude prevalence of OV infection was 24.5%, which was rather higher in men (27.6%) than in women (21.4%). There was not much difference according to age in men (range 26.0–29.6% in the four age groups), but prevalence increased with age in women (20.1% in age group 35–44 and 25.6% in age group 65–69). In those individuals who were infected, 33.5% (37.9% of men and 30.6% of women) had a heavy infection, with more than 1800 EPG.

Table 1 shows the number of individuals tested, the number positive for OV, the crude and adjusted proportions (sex and age) of the population infected (with 95% CI), by district and period. The number of CHCA cases and truncated age-standardized incidence rates are also shown.

Most districts were visited only once during the 12 years of recruitment. Only districts 1, 2 and 7 were surveyed in both the first and second period. A substantial reduction in the prevalence of infection was observed in districts 2 and 7 but not in district 1.

Figure 1 shows the simple correlation between the incidence of CHCA and the prevalence of OV infection for the 20 districts, both rates were age, sex and period adjusted. The Pearson's correlation coefficient (r) was 0.009 indicating no apparent association.

However, the number of subjects surveyed and the size of the population at risk varied greatly by district. Figure 2 plots the incidence of CHCA against the prevalence of OV infection for each district, age group and time period, with the weight illustrated by the area of the circles proportional to (number of OV tests) × (number of CHCA cases). The figure suggests a positive association between OV infection and CHCA incidence.

The results of Poisson regression analysis are given in Table 2. All factors were significantly associated with the incidence of CHCA, with age showing the strongest association. The incidence of CHCA was 2.5 times higher in those aged 65–69 years than in the youngest age group (35–44). The proportion of OV-infected individuals was significantly associated with the number of incident cases; the estimated coefficient for OV positivity predicts an increase in the incidence rates by 44 and 16/100 000 for every 1000 men and women, aged 65–69 years, respectively, for an increase in the prevalence of infection from 10% to 15%. Both sex and age were strong confounders of the association (details not shown). But more important for the association was the fact that the result takes into account the variable precision of the estimated incidence rates of CHCA and prevalence of OV infection. The log-likelihood of the Poisson model was slightly but not significantly lower when subjects considered positive were confined to those with an infection intensity of at least 600 EPG; the numbers of cases predicted by this model, when rounded to an integer, matched those predicted by the model in Table 2. Goodness-of-fit was, however, worse when the cut-off point was moved to higher levels of infection intensity.

Discussion

In an ecological study, prevalence of exposure (OV infection) and occurrence of disease (incidence of CHCA) should be estimated in the same individuals within each population unit. CHCA incidence was measured in the entire district population, while OV prevalence was estimated from a sample. However, we believe that once adjusted for sex and age, the samples were reasonably representative of the total (district) population, with respect to OV infection. For the most part, the sub-district(s) where the subjects were recruited were selected at random. Only one district (Muang, district 1) has a substantial urban population, while the three subdistricts from which subjects were recruited to the cohort (and from whom the OV prevalence was estimated) were in the more rural parts (although all three were close to the city).

The overall prevalence of OV infection in our subjects (24.5%) was very similar to that found in previous studies of the population of this region of Thailand (e.g. 24% by Jongsuksantigul *et al.* 1992). These earlier studies found that, in adults, prevalence is much the same in males and females, and is not strongly related to age (Upatham *et al.* 1982, 1984; Haswell-Elkins *et al.* 1991a; Haswell-Elkins *et al.* 1994), although infection intensity may increase with age, and heavy infection is more common in men. The similarity of the findings among the population recruited into the cohort study also implies that the population sampling was successful in obtaining a representative sample of adults, at least as far as OV infection is concerned.

The IARC (1994) concluded that there is sufficient evidence that infection with OV is a cause of CHCA of the liver in human beings, but that there is no association between infection with OV and risk of HCC. Recognized HCC were therefore excluded. However, histological

Table 1 Numbers of individuals tested, number positive for *Opisthorchis viverrini* (OV), crude and adjusted (by sex and age) proportion of infected adults, and incidence of cholangiocarcinoma (CHCA), by district and period in Khon Kaen, Northeast Thailand

District code	District name	Period of study†	No. of OV tested	No. of OV positive	Crude proportion of OV infected (%)	Adjusted proportion of OV infected (by age and sex) (%)	95% CI of adjusted proportion of OV infected	Cumulative number of CHCA cases	Crude incidence rate of CHCA*	Truncated incidence rate of CHCA*
1	Muang	1	149	43	28.9	26.4	18.7–37.3	598	92.4	132.3
1	Muang	2	1003	250	24.9	25.7	22.5–29.2	709	88.9	135.7
2	Ban Fang	1	65	46	70.8	70.9	59.3–84.6	88	83.8	115.8
2	Ban Fang	2	369	134	36.3	31.0	23.9–40.1	90	72.3	100.7
3	Phra Yun	2	336	53	15.8	17.3	11.5–26.0	145	169.9	218.0
4	Nong Rua	1	128	47	36.7	36.9	28.9–47.1	303	171.9	248.4
5	Chum Phae	2	992	254	25.6	26.3	22.3–31.2	285	93.6	135.1
6	Si Chomphu	2	830	212	25.5	20.7	16.4–26.2	241	142.8	205.0
7	Nam Phong	1	133	31	23.3	25.5	18.4–35.3	186	86.8	111.9
7	Nam Phong	2	1122	160	14.3	10.5	6.9–16.0	186	71.5	93.8
8	Ubol Ratana	2	563	102	18.1	19.5	14.4–26.6	78	81.2	111.6
9	Kranuan	2	97	2	2.1	10.0	2.7–37.2	260	117.4	184.6
10	Ban Phai	2	719	237	33.0	36.2	31.1–42.2	462	123.5	180.6
11	Puai Noi	2	363	46	12.7	11.2	7.6–16.5	86	206.1	302.1
12	Phon	2	1026	147	14.3	13.4	10.6–17.0	228	105.9	144.9
13	Waeng Yai	2	292	85	29.1	34.2	23.2–50.5	106	160.6	219.0
14	Waeng Noi	2	647	119	18.4	18.8	12.0–29.5	135	131.2	172.6
15	Nong Song Hong	2	471	77	16.3	18.7	14.3–24.6	187	105.1	155.2
16	Phu Wiang	1	336	138	41.1	37.8	32.3–44.1	443	208.9	293.2
17	Mancha Khiri	1	3884	809	20.8	21.5	20.1–22.9	465	215.7	288.6
18	Chonnabot	1	4059	1191	29.3	29.9	28.5–31.4	269	238.2	317.6
19	Khaosuankwang	2	692	142	20.5	18.6	14.7–23.4	90	117.9	162.1
20	Phu Pha Man	2	117	48	41.0	39.3	28.1–55.0	34	69.6	107.5

† 1 = 1990–1995; 2 = 1996–2001.
* per 100 000.

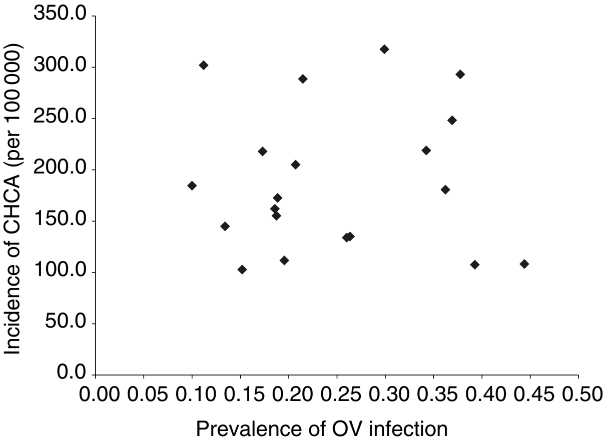

Figure 1 Simple correlation between the prevalence of *Opisthorchis viverrini* (OV) infection by district (age standardized), and the age-standardized incidence of cholangiocarcinoma (CHCA) in Khon Kaen, Northeast Thailand. Pearson's correlation coefficient (r) = 0.009.

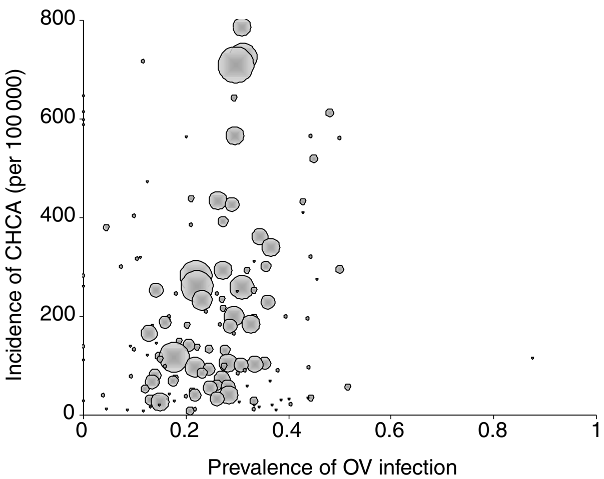

Figure 2 Graphical correlation between the prevalence of *Opisthorchis viverrini* (OV) infection by district, age group, sex and time period, and the incidence of cholangiocarcinoma (CHCA) in Khon Kaen, Northeast Thailand. Area of circles is proportional to (number of OV test) × (number of cases).

diagnosis is available for only a minority of liver cancer cases in Khon Kaen (5–6% in 1993–1997) (Parkin *et al.* 2002), as they are considered to be untreatable cancers, and so diagnostic efforts to distinguish between HCC and CHCA are of limited or no practical value. Nevertheless, in this high risk population, and based on the relative frequency of the two types in histologically diagnosed cases

Table 2 Results of Poisson analysis of number of annual incident cases with covariates, the prevalence of *Opisthorchis viverrini* (OV) infection, sex, age group, period and district in Khon Kaen, Northeast Thailand

Variables	Coefficient	SE	95% CI
OV positive	0.002	0.000	0.002 to 0.002
Age (years)			
5–44	1.0		
45–54	1.30	0.005	1.289 to 1.309
55–64	2.29	0.005	2.282 to 2.302
65–69	2.54	0.006	2.532 to 2.556
Sex			
Men	1.0		
Women	−0.987	0.003	−0.993 to −0.981
Period			
1990–1995	1.0		
1996–2001	−0.626	0.004	−0.633 to −0.618

(Parkin *et al.* 2002), eight of nine liver cancer cases are CHCAs. Moreover, it is very unlikely that there is substantial variation between districts in incidence of HCC, as aflatoxin exposure in this population is low (Srivatanakul *et al.* 1991), and prevalence of HBsAg is rather uniform in the different districts. Thus, the inter-district variation in liver cancer incidence very largely reflects variation in incidence of CHCA.

The first evidence for the association between OV infection and risk of CHCA came from case series, drawing attention to the coincidence of two diseases, normally rare, in the same geographic area and in the same individuals. Several case–control studies of CHCA and OV have subsequently been conducted. Kurathong *et al.* (1985) evaluated OV infection by faecal egg counts in 25 CHCA cases in comparison with other hospital patients. Because the cases had obstructive jaundice, relatively few CHCA patients were OV positive, so that no association could be observed. In the study by Parkin *et al.* (1991), 103 cases among inhabitants of Northeast Thailand were compared with a similar number of age- and sex-matched controls. Infection with OV (past or present) was estimated in terms of an increase in titre of antibodies in serum, as this is known to correlate with intensity of infection. A relative risk of 5.0 for an antibody titre >1:40 was found. There was, however, no association with the presence or absence of eggs in faeces. Haswell-Elkins *et al.* (1994) identified 15 asymptomatic cases of CHCA through a community screening programme. The prevalence of OV eggs in the faeces of these subjects could be compared with that in 1807 control subjects. The odds ratios associated with infection were 1.7 (95% CI 0.2–16.3) for ≤1500 EPG, and 14 (95% CI 1.7–119) for >6000 EPG.

Now that infection with OV can be readily treated with the drug praziquantel, which is well known and readily available to the population, the presence of eggs at a point in time may not give much idea about past infection. For this reason, antibody tests have been used to try to estimate past intensity of infection in individual-based studies, although they are not entirely satisfactory with respect to their specificities and sensitivities when compared with the conventional faecal examination (Haswell-Elkins *et al.* 1991b; Sirisinha *et al.* 1995). The study described in this paper is an ecological comparison, in which inference about the effect of OV infection on individuals is made from an observation at group level (the groups are districts of Khon Kaen). The inability of current faecal egg counts in individuals to reflect their past exposure to the parasite is one justification for this choice of study design. In addition, for infectious diseases, ecological estimates of effect may be more appropriate than in individual-based study designs, which assume that the outcome in one individual is independent of exposure and outcome in others in the same group (Koopman & Longini 1994). The outcome of OV infection may be better seen at group level, therefore, where individual exposure is better captured by measures of the intensity of infection in a population (related to a variety of factors in the parasite's life cycle, the environment, or in the other inhabitants) than by a single point measurement on the individuals themselves.

Previous correlation studies of OV infection and incidence of CHCA at the population level have been conducted in Thailand. Srivatanakul *et al.* (1991) compared five regions of Thailand, with respect to liver cancer incidence, and levels of anti-OV antibody and faecal egg counts in healthy volunteers from each. The correlation between the estimated incidence of CHCA and prevalence of antibody ≥1/40 was 0.98 ($P < 0.004$). The association with faecal egg count was less strong (0.53; $P = 0.35$). Within Khon Kaen province, Sriamporn *et al.* (1993) showed no difference by univariate simple comparison in the overall prevalence of infection between two districts with the highest and lowest incidence of liver cancer in 1988–1990. Similarly, a survey of villagers in Northeast Thailand showed a strong association between the intensity of OV infection and ultrasound-diagnosed abnormalities of the biliary tract that are associated with an enhanced risk of CHCA (Mairiang *et al.* 1992).

Conclusions

Incidence of CHCA in small geographic units, obtained by routine surveillance through cancer registration, is a useful method of describing risk associated with OV infection at population level.

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