RESEARCH COMMUNICATION

Gastric Cancer: the Roles of Diet, Alcohol Drinking, Smoking and *Helicobacter pylori* in Northeastern Thailand

Supannee Sriamporn[1], Veronica Setiawan[2], Paola Pisani[3], Krittika Suwanrungruang[1], Suchart Sirijaichingkul[4], Pisaln Mairiang[5], D Maxwell Parkin[3]

Abstract

The incidence of gastric cancer in the countries of South East Asia is variable, ranging from age-standardized rates of 20.9/10[5] (men) and 10.4/10[5] (women) in Hanoi, Vietnam to 4.1/10[5] (men) and 2.1/10[5] (women) in Khon Kaen, Thailand. The reasons for these differences are unknown. Possible explanations are differences in dietary habits, alcohol drinking, smoking and/or the prevalence of infection with *Helicobacter pylori* (*H. pylori*). A case-control study was conducted in Khon Kaen, Thailand, to study the role of these factors in gastric cancer carcinogenesis. 131 gastric cancer cases and 262 matched controls were recruited for the study. Information on dietary habits, alcohol drinking and smoking were collected by a structured questionnaire. Blood samples were available from 111 cases and 232 controls for *H. pylori* assay. Using an unconditional logistic regression model controlling for age and sex, we assessed the effects of dietary habits, alcohol drinking, smoking and *H. pylori* infection on the risk of gastric cancer. A high intake of salt (OR=1.8; 95%CI 1.1-3.0) and fermented foods (OR=1.9; 95%CI 1.1-3.3) was found to be associated with an increased risk. Preference for spicy food was not associated with gastric cancer risk in this population. Although there were negative associations between gastric cancer and vegetable and fruit intake, they were rather weak (OR 0.8 for both) and non significant. There were also weak (non-significant) associations with smoking and alcohol consumption, and no association with *H. pylori* infection (OR=0.6; 95%CI 0.4-1.0). Infection of *H. pylori* was associated with various indicators of crowding.

Key Words: Case-control status - stomach cancer - tobacco smoking - diet - *Helicobacter pylori*

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Introduction

Gastric cancer remains the third most frequent cancer in the world, despite the declining trend of incidence and mortality in most developed countries (Parkin et al., 2001). The highest incidence and mortality rates are found in Eastern Asia, but the incidence in the countries of South East Asia appears to be variable, ranging from age standardized rates of 20.5/105 (men) and 10.4/105 (women) in Hanoi, in the north of Vietnam to 4.1/105 (men) and 2.1/105 (women) in Khon Kaen, in the north east of Thailand (Parkin et al., 1997). In Thailand, the estimated age-standardized incidence in 1993 was 4.9/105 in men and 3.0/105 in women (Deerasamee et al., 1999).

Risk factors for stomach cancer include low intake of vegetables and fruits particularly citrus fruits, alcohol drinking and tobacco smoking. High consumption of salt and lack of refrigeration are possibly the most consistent and strongest determinants of the disease (WCRF, 1997). Other dietary items such as garlic may protect from the disease (You et al., 1989; Dorant et al., 1996), and monotonous diets high in starchy food pose an increased risk.

Helicobacter pylori infection has been accepted as being carcinogenic to humans (IARC, 1994). The evidence is largely based on sero-epidemiological studies, and the strength of the observed association is rather weak, particularly in developing countries (Muñoz and Pisani,

[1]Cancer Unit, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand, [2]Department of Epidemiology, University of California at Los Angeles, USA, [3]Unit of Descriptive Epidemiology, International Agency for Research on Cancer, Lyon, France, [4]Department of Immunology, Faculty of Associated Medicine, Khon Kaen University, Khon Kaen 40002, Thailand, [5]Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand
Corresponding author: Ms Supannee Sriamporn, Department of Epidemiology, Faculty of Public Health, Khon Kaen University, Khon Kaen 40002, Thailand - Tel: (66) 43-243088; Fax: (66) 43-243088; e-mail supannee@kku.ac.th

1994). The proportion of the population infected with *H. pylori* is large in developing countries - 80-90%; infection is contracted at a young age and persists throughout life (Forman, 1991). Acquisition is favoured by crowding/ interpersonal contact – and hence is linked to low socio-economic status. It is clear, therefore, that other co-factors need to be considered, such as the possibility that only some strains are involved in the carcinogenic process and/or the interaction with other factors (Xiang et al., 1995; Blaser et al., 1995; Muñoz and Franceschi, 1997).

As part of a multicentre study of gastric cancer in South East Asia, we studied possible determinants of gastric cancer in the population of Khon Kaen province in N.E. Thailand. Khon Kaen province is some 450 km north-east of Bangkok, and had a population of about 2 million in 2000. The population until recently was relatively poor (even by Thai standards), and largely engaged in agriculture based on rice cultivation.

The study is a hospital-based case-control study, investigating various aspects of diet, smoking, alcohol drinking and *H. pylori* in determining risk of gastric cancer. In addition, we also studied some factors of childhood history that may be associated with the transmission of *H. pylori* infection in this area. This study is a part of a multicentre study of gastric cancer in the South East Asian region.

Materials and Methods

Subjects

131 new gastric cancer cases were recruited from Srinagarind Hospital and Khon Kaen Regional Hospital, Khon Kaen Province, Thailand, between January 1996 and December 1997. All were from Khon Kaen or neighbouring provinces. Most cases were histologically (65%) or endoscopically (20%) confirmed, and were interviewed within 6 months of first diagnosis. In the same period, two controls were recruited for each case (a total of 262) matched by hospital, sex, age (± 5 years) and province of residence. Subjects with gastrointestinal disease were excluded. All subjects gave informed consent to their participation in the study; subjects who refused, were too old or unable to do the interview were excluded from the study. A 5 ml blood sample was obtained from 111 (84.7%) of the cases and 232 (88.5%) of the controls. The controls had a variety of diseases, the main ones being diseases of the eye (50), genito-urinary system (26) and fractures (14). There were 71 other cancers, the main ones being lip/oral cavity/pharynx (14), lung (12) and breast (11).

Interview

Subjects were interviewed by two trained interviewers, using a structured questionnaire. The questionnaire comprised two sections. The first section included demographic and socio-economic status, smoking history, allowing for various periods of different consumption, medical and childhood history. The second section was a food frequency questionnaire structured by meals. The interview referred to habits before the subjects became sick with their present illness (one year earlier). All subjects were reminded of this condition throughout the interview.

Measurement of Serum IgG to Helicobacter pylori

The presence of serum IgG antibodies against *Helicobacter pylori* were measured by enzyme-linked immunosorbent assay (ELISA) using Cobas Core Anti-*H.pylori* EIA. In the first step, serum was diluted and incubated with beads coated with *H. pylori* antigen to bind anti- *H.pylori* antibodies. Unbound materials were removed by washing, and in the second step, the antigen-antibody complex was detected with peroxidase conjugated goat anti human IgG antibody. After the removal of unbound conjugate, the beads were incubated with a substrate solution containing tetramethylbenzidine and hydrogen peroxide. The intensity of the blue colour that developed was proportional to the amount of *H. pylori* specific antibody bound to the beads. The enzymatic reaction was stopped by adding 5% sulfuric acid solution. The absorbance values were measured under wavelength of 450nm and the standard curve was constructed. The concentrations of anti-*H. pylori* IgG were then determined by interpolation of the standard curve. A cutoff of 20mg/ml was used to define the presence of infection.

Statistical Analysis

The relationships between gastric cancer and possible risk factors were measured using odds ratios (OR) and their 95% confidence intervals (CI) derived from unconditional logistic regression using STATA. All variables were categorized based on percentiles of the distribution in controls. Nonsmokers were subjects who had never smoked at least one cigarette per day for six-month period in their lives. All of the smoking analyses were done only for males because there was only one female who smoked in this study. In addition, controls (n=46) with diseases that were associated with smoking were excluded from the analyses. Smokers included those who smoked filtered, unfiltered cigarettes and yamuan (a home-made cheroot). Duration of smoking, and average number of cigarettes per year were computed based on all smoking periods reported and dichotomized on the median of the controls. The average number of cigarettes was calculated as annual cigarette consumption (filtered and unfiltered) plus 1.5* times annual yamuan consumption. The 1.5 correction factor was used to allow for the longer size of yamuan compared with the regular cigarettes. The type of cigarettes was divided into filtered and unfiltered categories. Yamuan was included in the unfiltered category.

For the analyses of alcohol drinking, controls (n=16) with diseases that were associated with alcohol drinking were excluded. There were two categories for alcohol drinking: drinkers and nondrinkers. For the alcohol drinkers, the duration and amount of drinking were categorized based on the 50th percentile of the controls, short (1-14 years) and long (> 14 years) habit. The drinking amount (in ml per

year) was calculated by adding all types of alcoholic beverages (beer, sato, white alcohol, maekong and other whiskies) consumed per year, and dichotomized into low (1-6960) and high (> 6960).

In traditional Thai cooking, salt is not added to dishes and a plain ingredient. Food dishes are seasoned with a variety of sauces, some of which are very salty and/or fermented. The dietary questionnaire assessed the consumption of typical sauces in association with each relevant food group by meal. The overall intake of salty food was then calculated as the frequency of use of salty sauces times that of the associated food, summed over all relevant food items/dishes. The intake of fermented food was obtained in a similar way, based on fermented sauces. Fish is often fermented, and is analyzed separately. Type of fish/shellfish consumption (frequency per year), freshwater or seawater, was dichotomized into low and high intake, based on the 50th percentile of the controls. Participants reported their preference for spicy or not spicy food.

In addition, some factors that might be associated with the transmission of *H. pylori* infection in childhood were studied. These factors were age, sex, income, number of siblings, number of persons in the household, and sharing of bed and/or bedroom. Subjects were asked whether their mother had fed them kaoyum as an infant (kaoyum is rice ± banana, pre-chewed by the mother). Age and sex were included in all of the models for the logistic analyses when calculating the ORs and the 95% Confidence Intervals (CI)s.

Results

Table 1 shows the distribution of general characteristics by case-control status. Since this is a matched case-control study, the distributions of age, sex and province of residence were the same in cases and controls. 60% were males and half were 55 years of age or older. Thirty-eight percent were from Khon Kaen province. The majority was married (84% of cases and 79% of controls). Most of subjects were Buddhist and spoke the local dialect.

Table 2 shows smoking habits in male cases and controls (excluding those with tobacco-related disease), and the odds ratios (OR) with their 95% confidence intervals (CI). There is a slightly higher risk (non-significant) of gastric cancer in smokers relative to non-smokers, and in smokers of unfiltered cigarettes compared to smokers of filtered cigarettes (non significant). There was no evidence of a dose-response effect with respect to duration of smoking or amount smoked.

Only 3 men were chewers of betel nut. When analysis was confined to females, 11 of 53 cases (20.8%) were chewers, compared with 26 of 97 controls (26.8%), equivalent to an O.R. of 0.6 (95% CI 0.3-1.5). There was no clear dose-response effect with respect to duration of the habit, or amount chewed.

Most cases (67/87) and controls (132/153) were non-drinkers (Table 2). The risk associated with alcohol consumption did not achieve statistical significance - O.R. 2.3 (95% CI 0.8-6.1) in drinkers of more than 14 years duration, relative to non-drinkers (Table 2). There was no trend in risk with frequency of alcoholic drinks consumed.

Table 3 shows frequency of consumption of salted and fermented foods, based on the food frequency questionnaire.

Table 1. The Distribution of General Characteristics of Gastric Cancer Cases and Controls

Characteristics	Cases N=131	(%)	Control N=262	(%)
Sex				
Male	78	(59.5)	156	(59.5)
Female	53	(40.5)	106	(40.5)
Age in years				
< 55 years	68	(51.9)	131	(50.0)
> 55 years	63	(48.1)	131	(50.0)
Marital status				
Single	5	(3.8)	13	(5.0)
Married	110	(84.0)	207	(79.0)
Divorced	3	(2.3)	12	(4.6)
Widowed	13	(9.9)	30	(11.5)
First Language				
Dialect	124	(94.7)	248	(94.7)
Thai	5	(3.8)	11	(4.2)
Chinese	2	(1.5)	1	(0.4)
Other	-		2	(0.8)
Religion				
Buddhist	129	(98.5)	260	(99.2)
Christian	2	(1.5)	2	(0.8)
Education Level				
None-HS incomplete	108	(82.4)	205	(78.2)
> HS	23	(17.6)	57	(21.8)
Occupation				
Farmar	81	(61.8)	164	(62.6)
Government Official	18	(13.7)	51	(19.5)
Commercial	14	(10.7)	9	(3.4)
General employee	2	(1.5)	14	(5.3)
Other or no occupation	6	(4.6)	17	(6.5)
Not specified	10	(7.6)	7	(2.7)
Family Income/month (Baht)				
0-2591 (low)	42	(32.1)	86	(33.0)
2592-6000 (medium)	46	(35.1)	90	(34.5)
> 6000 (high)	43	(32.8)	85	(32.6)
Province of Residence				
Khon Kaen	50	(38.2)	100	(38.2)
Sakolnakhorn	12	(9.2)	24	(9.2)
Mahasarakharm	11	(8.4)	22	(8.4)
Udonthani	8	(6.1)	16	(6.1)
Loei	7	(5.3)	14	(5.3)
Chaiyaphum	7	(5.3)	14	(5.3)
Nongbuolamphu	5	(3.8)	10	(3.8)
Nongkhai	6	(4.6)	12	(4.6)
Nakornphanom	4	(3.1)	8	(3.1)
Roi Et	4	(3.1)	8	(3.1)
Other	17	(13.0)	34	(13.0)

Table 2. Smoking Habits and Alcohol Drinking by Case-control Status for Males only; Odds Ratio (OR) and their 95% Confidence Intervals (CI)

	Cases	Controls	OR* & 95% CI
Smoking			
Duration			
Nonsmokers	8	18	1.0
Short (1-33 years)	26	37	1.6 (0.6-4.1)
Long (> 33 years)	25	36	1.6 (0.6-4.4)
			p for trend: 0.38
Amount (cig number/year)			
Nonsmokers	8	18	1.0
Low (1-5475) 1-15/day	40	54	1.7 (0.7-4.3)
High (> 5475) 16+/day	25	38	1.5 (0.6-3.9)
Type of cigarette			
Filtered	14	26	1.0
Unfiltered	42	63	1.3 (0.6-2.9)
Alcohol drinking			
Duration			
Nondrinkers	67	132	1.0
Short (1-14 years)	9	11	1.6 (0.6-4.2)
Long (> 14 years)	11	10	2.3 (0.8-6.1)
			p for trend: 0.17

*Adjusted for age

Using the low level as referent group, an O.R. of 1.8 (95% CI 1.1-3.0) was observed in consumers of higher levels of salty sauces. Using the consumers of lower amount of fermented foods as referent group, the O.R. associated with higher levels of consumption was 1.9 (95% CI 1.1-3.3).

There was a strong correlation between consumption of salted and fermented foods so that the effect of reciprocal adjustment weakened both associations (Table 3). Comparing high salt/high fermented food subjects, with low salt/low fermented food yielded an O.R. of 2.1 (95% CI 0.9-5.1).

A similar percentage of cases (74%) and controls (73.7%) reported preference for spicy food (O.R. 1.0). No association was found with consumption of fermented fish (pla ra) – a common component of many traditional dishes – nor with several sauces containing chili and fermented fish (jeaw prik, jeaw bong), insects or meat (O.R. for high vs. low frequency 0.9, 95% CI 0.4-2.4).

Table 3. Salt and Fermentation from Food Preparation by Case-control Status; Odds Ratio (OR) and their 95% Confidence Intervals (CI)

Frequency/year	Cases	Controls	OR* & 95% CI	OR** & 95% CI
Salted food				
Low (0-100.7)	32	100	1.0	1.0
High (> 100.7)	59	101	1.8 (1.1-3.0)	1.5 (0.9-2.6)
Fermentated food				
Low (0-95.3)	58	156	1.0	1.0
High (> 95.3)	33	45	1.9 (1.1-3.3)	1.6 (0.9-2.9)

*Adjusted for age and sex
** Adjusted for age, sex and each other

Table 4 . Vegetable Consumption (frequency per year) by Case-control Status; Odds Ratio and their 95% Confidence Intervals

Types of vegetables (Frequency/year)	Cases	Controls	OR* & 95% CI
All Vegetables (per year)			
Low (0-922)	99	200	1.0
High (> 922)	17	42	0.8 (0.4-1.5)
Pickled vegetables			
Low (0-40)	49	139	1.0
High (> 40)	57	84	2.0 (1.2-3.1)
Fresh vegetables			
Low (0-54)	58	118	1.0
High (>54)	48	105	0.9 (0.6-1.4)
Cooked vegetables			
Low (0-56)	63	118	1.0
High (>56)	47	111	0.8 (0.5-1.3)

* Adjusted for age and sex

Table 4 shows consumption patterns for vegetables, and associated odds ratios. There was no statistically significant association between consumption of vegetables as a whole by frequency (O.R. high vs. low 0.8 – 95% CI 0.4-1.5) or quantity (O.R. high vs. low 0.9 – 95% CI 0.6-1.4), nor when these were categorized as fresh or cooked. However, there was a significantly raised O.R. for consumption of pickled vegetables (O.R. 2.0, 95% CI 1.2-3.1), although this was not a frequent habit in the population.

Table 5 shows analyses of consumption of fish. This is a food item that is often salted and fermented in traditional preparations. There were two types of fish and shellfish: freshwater and seawater. Using the low intake group as the referent, ORs of 1.4 (95% CI 0.9-2.2) for freshwater and 1.7 (95% CI 1.1-2.7) for seafood were obtained. After controlling

Table 5. Fish/Shellfish Consumption by Case-control Status; Odds Ratios (OR) and their 95% Confidence Intervals (CI)

Types of food (frequency/year)	Cases	Controls	OR* & 95% CI	OR* * & 95% CI
Freshwater				
Low (0-168)	62	146	1	1
High (> 168)	55	111	1.4 (0.9-2.2)	1.2 (0.8-2.0)
Seawater				
Low (0-64)	55	148	1	1
High (> 64)	61	95	1.7 (1.1-2.7)	1.7 (1.1-2.7)

* Adjusted for age and sex
** Adjusted for age, sex and each other

Table 6. *Helicobacter pylori* Infection by Case-control Status; Odds Ratio (OR) and their 95% Confidence Intervals (CI)

	Cases	Controls	OR* & 95% CI
Anti-*Helicobacter pylori* antibody (IgG)			
No (< 20 m/ml)	79	138	1.00
Yes (> 20 m/ml)	32	94	0.6 (0.4-1.0)

* Adjusted for age and sex

for each other, the following ORs were obtained, 1.2 (95% CI 0.8-2.0) for freshwater fish/shellfish and 1.7 (95% CI 1.1-2.6) for seafood.

Table 6 shows the distribution of anti *Helicobacter pylori* antibody (IgG) titre by case-control status and the O.R. and 95% CI. Using the 'non-infected' group (antibody titre < 20 μg/ml) as the referent, an O.R. of 0.6 (95% CI 0.4-1.0) was obtained for *H. pylori* infection and gastric cancer. Table 7 examines infection status among the controls, in relation to variables that might be associated with the transmission of this infection. The number of siblings, bed and bedroom sharing and number of cohabitants were weakly associated with *H. pylori* infection, none of them achieving statistical significance.

Discussion

This case control study is part of an international collaborative study, investigating the large regional disparities of gastric cancer in South East Asia. Thailand in general, including the populous, but largely North East region, which was the setting for this study, is a low incidence area. Since there have been no previous studies of the subject, the reason for this must be largely speculative.

Table 7. Infection with *Helicobacter pylori*, in Relation to Factors that may be Associated with its Transmission; Odds Ratios (OR) and 95% Confidence Intervals (CI)

Factors	Infected N=94	Not infected N=138	OR* & 95% CI
Number of siblings			
0-4	26	44	1.0
5-7	40	65	1.1 (0.6-2.2)
>8	28	29	1.9 (0.9-3.9)
			p for trend: 0.11
Fed by kaoyum			
No	6	9	1.0
Yes	87	126	1.2 (0.4-3.4)
Share bedroom			
No	9	17	1.0
Yes	85	121	1.4 (0.6-3.3)
Share bed			
No	11	19	1.0
Yes	83	119	1.3 (0.6-2.8)
Number of cohabitants			
0-3	28	40	1.0
4-5	38	64	0.8 (0.4-1.6)
>6	28	34	1.2 (0.6-2.5)

* Adjusted for age and sex

The North East region has been, for many decades, the most impoverished part of Thailand. Until the introduction of various industries in the last 10-20 years, the population was very largely rural, relying on the cultivation of rice as the staple crop; more recently, cassava and sugar cane cultivation has been introduced. Until recently, too, the birth rate was relatively high, resulting in large family sizes, and necessitating considerable out-migration from the area, to Central Thailand, or overseas.

It is somewhat surprising that infection with *Helicobacter pylori* was not found to be a risk factor within the population. Indeed, prevalence of infection, as judged by elevated anti-HP antibody titre, was lower in cases than in controls. Although there was some association between the presence of anti-HP antibody and indicators of crowding in childhood – which has been shown to be an important determinant of infection elsewhere (Barker et al., 1990; McCallion et al., 1996; Mendall et al., 1992) – none achieved formal statistical significance, and the prevalence of infection (as judged by anti-HP antibody) was low (40.5%).

There are several possible reasons for the observed negative association between *H. pylori* and gastric cancer. First, it has been argued that past exposure to *H. pylori* in gastric cancer cases tends to be underestimated (Muñoz, 1994), because *H. pylori* do not colonize or infect severely disrupted metaplastic or neoplastic epithelium. The bacterial load in gastric cancer cases showing extensive areas of intestinal metaplasia would therefore be low, and, in consequence, the anti-*H-pylori* IgG level of the cases may also be below the threshold set as positive for infection (20μg/ml). Gastric cancer patients (but not control subjects) would therefore be misclassified as seronegative, even though they had been infected in the past. This differential misclassification leads to under-estimation of the OR that can reverse a positive association into a negative one, making *H. pylori* appear to protect from gastric cancer. In a prospective study of gastric cancer in Shanghai, cases diagnosed within the first six years from recruitment did not show greater prevalence of *H. pylori* compared with a suitable sample of the cohort that remained free of the disease in the same time period (Webb et al., 1996). But cases diagnosed afterwards, in a longer follow-up after blood collection did show a significantly higher prevalence of infection (Yuan et al., 1999).

Second, the commercial test kits used to measure *H. pylori* infection in this population may not represent the local strain of *H. pylori*. In the above-mentioned cohort study in China (Yuan et al., 1999), an ELISA was developed using a local strain and validated in the study population, showing a significantly higher sensitivity compared to the commercial test in the first analysis (Webb et al., 1996). An earlier study in Thailand found that the validity of ELISA test to detect

H. pylori infection among patients with dyspepsia was improved when local bacterial strains were used (Bodhidatta et al., 1993). Insensitivity of the commercial test kit to detect HP infection may well have been present in our study, given the low prevalence of "infection" in the control population. Nevertheless, even with an insensitive test, the misclassification of HP infection would be non differential, leading to the observed association between HP and stomach cancer being biased towards the null. Finally, previous studies in populations with a high prevalence of infection with HP have failed to show a clear excess risk (Setiawan et al., 2000), because of lack of power to detect rather small relative risks when exposure prevalence in control subjects is high.

Five decades of research into the role of different dietary factors in promoting or preventing gastric cancer have resulted in a broad consensus that fresh fruit and vegetables are protective, while preserved, salted and pickled foods enhance risk (WCRF, 1997). Cereals, including rice, have been found to be associated with increased risk in some studies, although the WCRF report considers such evidence "inconclusive". On this basis, there is little reason to conclude that the low risk of gastric cancer in NE Thailand is a consequence of a "healthy" diet. Typically, the local diet is based on consumption of sticky rice, which is flavoured with various sauces, which often have fermented ingredients, are typically rather salty, and spiced with liberal use of chilli. Some proteins may be added in the form of fish (generally small fish caught in rivers and ponds); consumption of meat is rare and confined mainly to children. Vegetable consumption is commonly in the form of salads, again flavoured with salty, fermented, spicy sauces. Fruit consumption has not been common, except as incidental snacks (especially banana).

We assessed the role of salt intake and consumption of fermented foods from the food frequency questionnaire. Salt has been indicated as a risk factor for gastric cancer in many previous studies (Lee et al., 1995; Nazario et al., 1993; Sun et al., 2002), and this was confirmed in our study. Fermentation of foods (especially, in the local context, fish (pla ra, pla jom, pla som), and pork (sai grog) involves the production of nitrosamines. This compound has been implicated as a risk factor for gastric cancer in many studies (Buiatti et al., 1990; Shi et al., 1991), and frequent consumption of fermented food was a risk factor in our study. However, evaluation of this variable involved rather approximate categorization of individuals, based on recalled consumption patterns. To further investigate the association between fermentation and gastric cancer, more comprehensive and detailed data are required. Since the use of salt and fermentation in Khon Kaen food preparations were strongly interrelated, we were unable to clearly separate the independent effects of the two variables.

In view of its ability to produce gastritis (Myers et al., 1987) consumption of chilli has been suspected as possibly enhancing risk of gastric cancer. Studies in Mexico (Lopez-Carillo et al., 1994) and India (Gajalakshmi et al., 1996; Matthew et al., 2000) – both notably low risk areas for gastric cancer – have found increased risks associated with higher levels of chilli consumption. On the other hand, in Italy, Buiatti et al. (1989) found a decreased risk (O.R. 0.6) for higher consumption of chillies. We found no association within the population with stated preference for spicy and "not spicy" food – although it could be that chilli consumption even in the "not spicy" category is high by western dietary standards.

We observed slightly protective effects of vegetable, fruit and meat intakes. However these associations were not precise due to the fact that most of our subjects had similar eating habits, thus limiting the ability to assess even the slightest effects of these variables.

When vegetable consumption was divided into three categories (pickled, fresh and cooked), we observed a positive association between pickled vegetable consumption and the risk of gastric cancer. Both fresh and cooked vegetable consumption was negatively associated with the risk of gastric cancer. Vegetable consumption has been shown to be protective against gastric cancer in many studies (Correa et al., 1985; Jedrychowski et al., 1986; Sun et al., 2002; You et al., 1988). Pickled vegetables have, however been found to be a risk factor (Hoshiyama et al., 1992; Ramon et al., 1993; Sun et al., 2002). Fruit consumption in our study was found to be protective, although the association was weak and maybe due to chance alone.

Consumption of fish/shellfish was found to be positively associated with the risk of gastric cancer, especially the seafood. This may be due to the high salt content and the use of fermentation of seafood from the preservation process. An increased risk of gastric cancer among smokers has been observed in numerous studies, both case-control and cohort (Ji et al., 1996; Trédaniel et al., 1997; Zhang et al., 1996; Matthew et al., 2000). However, the lack of association that is often observed in hospital-based case-control studies (Agudo et al., 1992; Boeing et al., 1991; Jedrychowski et al., 1993; Rao et al., 2002) may be due to the high prevalence of smoking related diseases in the control series. For this reason, we excluded from the control group subjects with diseases that were related to smoking. A rather weak and statistically non-significant association with smoking was observed; duration of smoking, rather than amount smoked, providing a better indicator of risk.

Betel nut chewing used to be common in women in NE Thailand. We found a negative association with gastric cancer, although studies in India, where it remains a frequent habit, have not shown any effect on gastric cancer risk (Matthew et al., 2000; Rao et al., 2002). Betel leaf extract has been shown to inhibit the mutagenic effect of benzo(a)pyrene and dimethylbenz(a)anthracene (Nagabhushan et al., 1987), and tobacco-specific nitrosamines in mice (Bhide et al., 1991). However, betel nut chewing is gradually dying out in Thailand, and the number of chewers in our study was small, limiting the power to detect a clear association between betel nut chewing and gastric cancer.

After excluding the controls with diseases that were related to alcohol drinking, we observed that duration of alcohol drinking was positively associated with gastric cancer. As for smoking, duration seems to be a better predictor of the effect of alcohol than the amount of alcohol consumed. Many studies have investigated the role of alcohol drinking in gastric cancer carcinogenesis, but the results remain inconclusive (Ji et al., 1996; Zhang et al., 1996; Rao et al., 2002).

In conclusion, our study confirmed the protective effects of a high intake of fruit and vegetables on gastric cancer risk. The type of vegetable consumed was important; pickled vegetables were positively associated but cooked and raw vegetables were negatively associated with gastric cancer risk. We also observed a slightly higher risk for smokers and alcohol drinkers compared to the nonsmokers and nondrinkers. Food preparations commonly used in Khon Kaen, with relatively high salt levels and the use of fermentation, were positively associated with the risk of gastric cancer. Fish/shellfish consumption especially seafood was positively associated with the risk of gastric cancer. *H. pylori* infection was not a risk factor for gastric cancer in our study.

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