Familial Predisposition to Precancerous Gastric Lesions in a High-Risk Area of China[1]

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Abstract

Aggregation of intestinal metaplasia and dysplasia was investigated among families participating in a population-based gastroscopic screening survey in an area of China with one of the world's highest rates of stomach cancer. The prevalence of gastric dysplasia was significantly increased among those with dysplasia among siblings or spouses, but not parents. The odds of dysplasia were nearly doubled if an eldest brother or a spouse was affected. Sibling and spousal associations for intestinal metaplasia were much less pronounced and not statistically significant. The specificity of the findings suggests that familial risk of advanced precancerous lesions (dysplasia) is influenced not only by genetic factors, but also by environmental factors operating in childhood and early adult life.

Introduction

Although incidence rates have fallen dramatically over the past several decades in most industrialized countries, stomach cancer remains the leading cause of cancer mortality in China (1–4). Linqu, a rural county in Shandong Province, northeast China, has one of the world's highest mortality rates of stomach cancer (70 per 100,000 for men and 25 per 100,000 for women) and a high prevalence of precancerous gastric lesions (5, 6). Epidemiological studies in this endemic area have pointed to dietary factors (e.g., high intake of fermented pancakes and salt and low intake of fresh vegetables and fruits) and cigarette smoking in the development of both stomach cancer and its precancerous lesions (5, 7). Familial susceptibility to stomach cancer has also been found (5). Herein we examine familial aggregation of precancerous gastric lesions to provide further clues

to the role of environmental and genetic factors in the process of gastric carcinogenesis in this high-risk area.

Materials and Methods

The study was conducted among individuals who participated in a population-based stomach cancer screening program described in detail elsewhere (6). In brief, a total of 3433 subjects, representing 83% of eligible residents aged 35–64 (years) in 14 villages selected at random within four townships of Linqu County, were interviewed using a structured questionnaire and had a blood sample collection along with physical and gastroscopic examinations. The questionnaire sought information on cigarette smoking, diet, family and medical history, and other variables. During the gastroscopic examination, seven biopsies were taken from standard locations: two in the body; one in the angulus; and four in the antrum. Standardized histological diagnoses determined the presence or absence of superficial gastritis, chronic atrophic gastritis, intestinal metaplasia, or dysplasia for each biopsy. We then classified all subjects into four categories of superficial gastritis/chronic atrophic gastritis, intestinal metaplasia, dysplasia, and stomach cancer on the basis of the most severe lesion found in one of the seven biopsy specimens.

For each participant, information on the pedigree for his/her family was collected from village population rosters. Subjects who belong to the same family were identified and the kinship relation of each participant was recorded. Females born in the area generally married men outside their village, so that sibships among the age 35–64 study participants were typically all male.

We calculated ORs[4] as the measure of association between the prevalence of intestinal metaplasia and dysplasia in a study participant and whether his/her parents, siblings, or spouses had these lesions. Because only 13 stomach cancers were detected in the screening population, we excluded them from the analysis. Among siblings, the eldest brother's gastric status was used as the index, with ORs of intestinal metaplasia and dysplasia among any younger sibling determined according to whether the eldest brother had intestinal metaplasia or dysplasia. For married couples, risks of intestinal metaplasia and dysplasia were estimated separately for husbands and wives according to their spouses' gastric status. ORs were obtained by logistic regression adjusting for age, blood type, cigarette smoking, sour pancake consumption, and serum IgG antibody positivity to *Helicobacter pylori* infection—previously identified risk factors for dysplasia (8). In the OR calculations, risks of intestinal metaplasia and dysplasia were assessed relative to subjects with

[4] The abbreviations used are: OR, odds ratio; CI, confidence interval.

superficial gastritis/chronic atrophic gastritis, since only 1.5% of the subjects had all biopsies showing normal mucosa or superficial gastritis. Familial concordance in risk factor prevalence was assessed using kappa statistics (9).

Results

Familial relationship data and histological diagnoses were available for a total of 3235 participants (94.2% of the screenees), with 1718 (53.1%) males and 1517 (46.9%) females. The mean ages were 46.7 years for males and 45.7 years for females. Nearly all the men (98.1%) and the majority of the women (84.8%) were born in Linqu County. Superficial gastritis/chronic atrophic gastritis was the most advanced diagnosis for 1512 (46.7%), intestinal metaplasia for 1069 (33.0%), and dysplasia for 654 (20.2%). Almost all those with dysplasia also had concomitant intestinal metaplasia.

Review of family rosters identified a total of 1401 family units among the study participants. Thirty-nine % of the families had just one person, 28% had two, and 33% had three or more persons. The numbers of families having one, two, or three generations, respectively, were 1222 (87.2%), 176 (12.6%), and 3 (0.2%). There were 127 families with both a parent and a child, 365 with 2 or more siblings (average sibship size was 2.2), and 1027 husband-wife pairs.

Table 1 shows odds ratios for intestinal metaplasia as the most advanced lesion (*i.e.*, without dysplasia) and for dysplasia among those with a parent, sibling, or spouse with dysplasia. No significantly increased risks of intestinal metaplasia or dysplasia were found among persons who had a parent with dysplasia (results were similar whether the father or mother had dysplasia). In fact, risk of dysplasia was decreased in this group. Among the larger number of families with 2 or more siblings represented, however, the risk of dysplasia was significantly increased among persons whose eldest brother had dysplasia (OR, 2.2; 95% CI, 1.0–4.9), but there was little increase in intestinal metaplasia. Risks of dysplasia were significantly increased among wives whose husbands had dysplasia (OR, 1.9; 95% CI, 1.1–3.1), and among husbands whose wives had dysplasia (OR, 1.5; 95% CI, 0.9–2.5), with little association for intestinal metaplasia without accompanying dysplasia.

Table 2 shows odd ratios among men according to a combination of their eldest brothers' and their wives' gastric status. The odds ratio for dysplasia reached 6.7 (*P* < 0.05) among subjects whose eldest brothers and wives both had dysplasia: two-thirds (6/9) of those having a sibling and spouse with dysplasia themselves had dysplasia, compared to 19% (25/129) where neither the eldest brother nor wife had dysplasia.

Among second-degree relatives in the study population, we did not find that having an uncle with dysplasia increased the risk of dysplasia for nephews, nor did we find concordance of the gastric lesions among cousins (data not shown).

Table 3 shows familial concordance in the prevalence of risk factors for dysplasia in this population. Smoking was correlated among siblings (husband/wife concordance was not assessed because few women smoked). There was a strong familial concordance in sour pancake consumption, both for siblings and spouses. *H. pylori* antibody positivity

was positively but not significantly correlated among siblings and among spouses.

Discussion

Epidemiological evidence indicates that environmental factors play a major role in gastric carcinogenesis, which is generally thought to involve stepwise transitions from normal gastric mucosa to chronic atrophic gastritis, intestinal metaplasia, and dysplasia prior to cancer onset (10). A familial tendency to stomach cancer has been well-documented, but only limited data exist on familial predisposition to the precursor states and their transition from less to more advanced lesions. In a high-risk area of Colombia, having a mother with chronic atrophic gastritis was found to be an important risk factor for chronic atrophic gastritis, consistent with a genetic predisposition to early stages leading to cancer (11). We have previously shown in the present study population that having blood type A conferred a higher risk of intestinal metaplasia and dysplasia, suggesting a genetic component to the more advanced precursor lesions (7).

Our gastroscopic screening investigation in this very high-risk population living in a relatively remote, rural area of China provided an opportunity to assess familial risks of precancerous gastric lesions. Since nearly all adults were affected with chronic atrophic gastritis, we could not assess risk factors for the development of chronic atrophic gastritis from normal gastric mucosa. Our evaluations of intestinal metaplasia and dysplasia, however, indicate that the presence of dysplasia in a sibling or spouse was associated with a significantly increased risk of dysplasia, while the presence of dysplasia in a parent was not. The odds of dysplasia were more than doubled when the eldest brother was affected, and increased nearly two-fold when the spouse was affected. No significant familial associations were found for intestinal metaplasia without accompanying dysplasia. These findings suggest that shared environmental factors operating from childhood to adult life may contribute to the risk of progression to dysplasia. These factors include not only the dietary components implicated in this population (5, 7), but also infection by *H. pylori* which is generally felt to contribute to the development and progression of precancerous gastric lesions (10, 12).

In Linqu, women typically marry at about age 20 and then move to their husbands' families. Conversely, men tend to marry women from outside their village, although still usually from within Linqu County. Except for smoking, the lifestyle habits including diet are generally similar between spouses in this area. Thus the concordance of dysplasia between couples suggests that progression of chronic atrophic gastritis to dysplasia is at least partly determined by environmental factors. We previously reported that cigarette smoking and intake of sour pancakes were associated with elevated risks of dysplasia (7). Few women smoked, so we could not assess spousal concordance in smoking, but there were strong husband-wife correlations in sour pancake consumption that could contribute to the spousal aggregation of dysplasia. Among siblings, patterns of both cigarette smoking and sour pancake consumption were concordant. In addition, *H. pylori* infection, linked to the onset of gastritis which may start the progression toward cancer (12), also clustered in families. Although not significant, the concordance in *H. pylori* infection was somewhat stronger between siblings than spouses, suggesting the

Table 1   Odds ratios of intestinal metaplasia and dysplasia among those with dysplasia in a parent, sibling, or spouse

	SG/CAG[a]		IM[a]			DYS[a]		
	n	OR	n	OR[b]	95% CI	n	OR	95% CI
Parent DYS								
No	36		24			21		
Yes	26	1.0	12	0.7	0.3–1.9	8	0.3	0.1–0.9
Eldest brother DYS								
No	127		85			53		
Yes	35	1.0	24	1.4	0.6–3.0	41	2.2[c]	1.0–4.9
Husband DYS								
No	433		247			94		
Yes	109	1.0	93	1.4	0.9–2.1	51	1.9[c]	1.1–3.1
Wife DYS								
No	375		305			202		
Yes	55	1.0	39	0.8	0.5–1.3	51	1.5	0.9–2.5

[a] SG/CAG, superficial gastritis/chronic atroptic gastritis; IM, intestinal metaplasia without accompanying dysplasia; DYS, dysplasia.
[b] ORs adjusted for age, cigarette smoking, sour pancakes, *H. pylori*, and blood type.
[c] $P < 0.05$.

Table 2   Odds ratios of intestinal metaplasia and dysplasia among men according to the occurrence of dysplasia in a sibling and/or wife

Eldest brother DYS	Wife DYS	SG/CAG[a]	IM[a]			DYS[a]		
		n	n	OR	95% CI	n	OR	95% CI
No	No	56	48	1.0		25	1.0	
	Yes	9	6	0.8	0.3–2.3	7	1.7	0.6–5.2
Yes	No	19	13	0.8	0.4–1.8	19	2.2[b]	1.0–4.9
	Yes	2	1	0.6	0.1–6.6	6	6.7[b]	1.3–35.6

[a] SG/CAG, superficial gastritis/chronic atroptic gastritis; IM, intestinal metaplasia without accompanying dysplasia; DYS, dysplasia.
[b] $P < 0.05$.

Table 3   Familial concordance in risk factors for dysplasia

Factor	Younger brother	Elder brother		Wife	Husband	
		No	Yes		No	Yes
Smoking						
	No	16	47			
	Yes	43	256			
	Concordance = 0.75; K = 0.11[a]					
Sour pancake consumption						
	No	267	22	No	747	50
	Yes	16	60	Yes	35	195
	Concordance = 0.89; K = 0.69[b]			Concordance = 0.91; K = 0.76[b]		
H. pylori positive						
	No	115	63	No	235	164
	Yes	74	70	Yes	238	225
	Concordance = 0.57; K = 0.13			Concordance = 0.53; K = 0.06		

[a] $P < 0.10$
[b] $P < 0.01$.

importance of early onset of the infection. The highest odds of dysplasia (OR, 6.7) occurred among subjects who had both an eldest brother and a wife with dysplasia. The numbers of such cases were relatively small, but the trend suggests that risk is increased by extended duration of shared exposure from childhood to adult years. No significant associations were found for second-degree relatives, who typically do not share a home environment.

It should be noted that having a parent with dysplasia did not significantly increase the risk of dysplasia among offspring, but having a parent with stomach cancer did (7). In the present study, however, for a parent-child combination to be included, both must have been in the 35–64 age range. Hence the parents were generally 55–64 while the children were typically 35–44, and we could evaluate parent-child dysplasia concordance only over a limited age

range, whereas data on familial stomach cancer were not restricted by age. In addition, since dysplasia is a risk factor for stomach cancer and since stomach cancer is usually fatal, parents who were participants in the study may have been less likely to have dysplasia. Such a competing risk phenomenon may have contributed to the lower ORs observed.

There are some further limitations in our data. Because the subjects were between 35 and 64 years of age, for some families only a minority of their members were study participants, and most of the family units involved only one or two generations, with only a few spanning three generations. Because most women married out of their home villages while men remained, almost all the offspring, siblings, and cousins in the study population were males. Finally, despite the relatively large number of subjects and comparatively high (20%) prevalence of dysplasia, when we calculated the risks of intestinal metaplasia or dysplasia by the relatives' status, the number of cases often was relatively small, especially for mother-offspring pairs. Nevertheless, this population-based gastroscopic screening study among healthy adults in Linqu County was able to detect a familial tendency to dysplasia affecting both siblings and spouses. This pattern suggests that environmental as well as genetic factors are involved in the progression of precancerous gastric lesions.

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