



EVOLUTION OF PRECANCEROUS LESIONS IN A RURAL CHINESE POPULATION AT HIGH RISK OF GASTRIC CANCER

Wei-Cheng You^{1*}, Ji-You Li², William J. BLOT³, Yun-Sheng CHANG², Mao-Lin JIN², Mitchell H. GAIL¹, Lian ZHANG², Wei-Dong LIU⁴, Jun-Ling MA², Yuan-Ren HU⁵, Steven D. MARK¹, Pelayo CORREA⁶, Joseph F. FRAUMENI, JR.¹ and Guang-Wei XU²

¹National Cancer Institute, Bethesda, MD, USA

²Beijing Institute for Cancer Research and School of Oncology, Beijing Medical University, Beijing, China

³International Epidemiology Institute, Rockville, MD, USA

⁴Linqu Public Health Bureau, Linqu, Shandong, China

⁵Westat, Inc., Rockville, MD, USA

⁶Louisiana State University Medical Center, New Orleans, LA, USA

The pathogenesis of gastric cancer (GC), particularly of the intestinal type, is thought to involve a multistep and multifactorial process. Our objective was to determine the rates of transition from early to advanced gastric lesions in a population in Linqu County, China, where the GC rates are among the highest in the world. An endoscopic screening survey was launched in 1989–1990 among 3,399 residents aged 34–64 years with precancerous lesions diagnosed from biopsies taken from 7 standard locations in the stomach and from any suspicious sites. The cohort was subsequently followed, with endoscopic and histopathologic examinations conducted in 1994. Logistic regression analysis was used to estimate odds ratios (ORs) of progression to advanced lesions of various levels of severity as a function of age, sex and baseline pathology. The rates of progression were higher among older subjects, among men and among subjects with more extensive gastric lesions. 34 incident GCs were identified during the follow-up period. The ORs of GC, adjusted for age and sex, varied from 17.1, for those with baseline diagnoses of superficial intestinal metaplasia (IM), to 29.3, for those with deep IM or mild dysplasia (DYS) or IM with glandular atrophy and neck hyperplasia, to 104.2, for those with moderate or severe DYS, as compared with subjects with superficial gastritis (SG) or chronic atrophic gastritis (CAG) at baseline. Our prospective study of a high-risk population revealed sharp increases in the risk of GC and advanced precursor lesions according to the severity of lesions diagnosed at the start of follow-up. *Int. J. Cancer*, 83:615–619, 1999.

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Over the past 2 decades there has been increasing evidence from clinical and population surveys (Kato *et al.*, 1992; Filipe *et al.*, 1994; Ruge *et al.*, 1994) that the pathogenesis of GC, particularly of the intestinal type, involves a multistep and multifactorial process (Correa, 1988; Siurala, 1981; Muñoz and Matko, 1972). However, there is little data available to quantify the risk of transition from early to advanced gastric lesions. In 1989, a large population-based survey of precancerous gastric lesions was conducted among 3,399 residents aged 35–64 years in a rural area of Shandong Province, China with one of the world's highest rates of GC (You *et al.*, 1993). CAG affected nearly the entire adult population, with IM detected in nearly half and DYS in 20%. A linear relationship between age and prevalence of IM and DYS was found, suggesting that these lesions accumulate and progress with advancing age (You *et al.*, 1993). This population has been followed since 1989, with a repeat endoscopic examination conducted in 1994. In a preliminary report, we described the odds ratios (ORs) of GC among subjects with baseline diagnoses of IM and DYS compared with CAG in this cohort (You *et al.*, 1995). We herein report new information on the transition rates of precancerous gastric lesions and their progression to GC among subjects with superficial IM, deep IM or mild DYS or IM with glandular atrophy and neck hyperplasia, and moderate or severe DYS, as compared with SG/CAG, at baseline.

MATERIAL AND METHODS

The design of the baseline endoscopic screening survey is described in detail elsewhere (You *et al.*, 1993). In brief, 3,399 residents, aged 35–64 years, from 14 villages within four townships of Linqu County, representing 83% of the eligible population were enrolled between 1989 and 1990. All participants were given a brief physical examination and their medical histories recorded. The subjects received a gastroscopic examination, with biopsies taken from 7 standard sites in the stomach: 4 from the antrum, 1 from the angulus, and 1 each from the lesser and greater curvatures of the body of the stomach. If any suspicious areas were seen, additional biopsies were taken. Each slide was reviewed by a panel of 3 senior pathologists at the pathology laboratory of the Beijing Institute for Cancer Research (BICR). Pathologic diagnoses were based on criteria proposed by the Chinese Association of Gastric Cancer, published along with photographs of precancerous lesions, in an earlier article (You *et al.*, 1993). Briefly, the diagnostic criteria for each histologic classification are described as follows: A. Normal: The gastric mucosa was normal histo-pathologically. B. SG: For convenience, all non-atrophic gastritis was placed in this category. The lamina propria is infiltrated by plasma cells, lymphocytes and occasional eosinophils, without glandular atrophy. Degenerative and regenerative changes and, in some instances, simple hyperplasia of superficial epithelial cells are present; however, the morphology of the cells is essentially normal. Polymorphonuclear leukocytes are seen in the lamina propria, pits and epithelium, indicating chronically active gastritis. C. CAG: Glandular morphology disappears partially or completely in the mucosa, replaced by connective tissue. Inter-glandular spaces are infiltrated mainly by plasma cells and lymphocytes. Polymorphonuclear leukocytes may be seen in the glandular epithelium and lumen, indicating active disease. Each type of CAG is graded as mild or severe, depending upon the extent of disappearance of glandular morphology in the mucosa. D. IM: Gastric glandular mucosa is replaced by mucosa resembling that found in the intestines. Goblet cells in tubular glands are the main histologic feature. IM was graded as superficial, involving the surface epithelium and pits, or deep, involving the deep pepsinogen-secreting portion of the gastric glands. E.

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*Correspondence to: Division of Cancer Epidemiology and Genetics, National Cancer Institute, EPS Room 8030, 6120 Executive Boulevard, Bethesda, MD, 20892-7244 USA. Fax: 1 301 402-0081. E-mail: youw@exchange.nih.gov

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DYS: Cellular atypia, abnormal differentiation and disorganized mucosal architecture are the main morphologic features. Based on the degree of these changes, dysplasia was graded as mild, moderate or severe.

Each biopsy was classified according to the presence or absence of SG, CAG (mild or severe), IM (superficial, deep or IM with glandular atrophy and neck hyperplasia), DYS (mild, moderate or severe) or GC. If GC was diagnosed, baseline material on the same subjects was re-examined. Each biopsy was given a diagnosis based on the most severe histology found in the biopsy, and each subject was assigned a "global" diagnosis based upon the most severe diagnosis among any of the biopsies.

The participants have been followed up since 1989–1990, with systematic monitoring of deaths and cancer occurrences. To detect an early GC among subjects with more advanced lesions, 672 individuals with DYS or extensive IM diagnosed at baseline received a second endoscopic examination in the spring of 1992. In the autumn of 1994, a repeat endoscopic examination was offered to all the cohort members. The reasons for non-participation were recorded, but no further attempts were made to enroll those who did not wish to participate. Subjects who had blood clotting disorders, high blood pressure, liver disease or chronic obstructive pulmonary disease were excluded from further examination. The 1994 survey employed the same endoscopic and histopathologic procedures as in 1989, and histo-pathologic diagnoses were made by the same pathologists who conducted the 1989 survey, but the pathologists were blinded as to the baseline diagnoses. One slide each from 200 randomly selected subjects in the study population and, in addition, the next single slide with their presumptive diagnosis: 30 cases with GC and 40 cases with DYS in the study population were reviewed by Drs. Ji-you Li, professor and chief pathologist at BICR, and Pelayo Correa, professor and chief pathologist at Louisiana State University, experts on gastric pathology from China and the United States, respectively. Among 270 slides, consensus was reached by the 2 pathologists on the diagnoses of 267 slides; Dr. Li diagnosed the remaining 3 slides as mild DYS, while Dr. Correa identified them as borderline DYS.

The cohort was divided into 6 groups based on baseline pathology: 1. SG or mild CAG ($n=1,032$, only 48 of which were SG); 2. severe CAG ($n=208$); 3. superficial IM ($n=256$); 4. deep IM (586); 5. mild DYS ($n=503$) and 6. moderate or severe DYS ($n=43$, only 3 of which were severe DYS). For each of the 6 baseline groups, the proportion whose diagnoses stayed the same and the proportion who changed to any other histo-pathology in 1994 were calculated. For the GC risk analysis, we combined deep IM, mild DYS and IM with glandular atrophy and neck hyperplasia into one category.

Three logistic regressions were performed to estimate the ORs of progression to more advanced lesions (Breslow and Day, 1980). First, the OR for progression to superficial IM and above was estimated for those with severe CAG compared with SG/mild CAG. Second, ORs for progression to deep IM or above were

estimated for those with severe CAG and superficial IM compared with SG/mild CAG. Third, ORs for progression to DYS or GC were estimated for those with severe CAG, superficial IM and deep IM compared with SG/mild CAG. In the last logistic regression model, we also performed a test to examine trends of progression, with baseline severe CAG, superficial IM and deep IM scored as 0, 1 and 2, respectively. Each model included gender and age as covariates in addition to baseline histo-pathology.

A multiple logistic regression analysis was performed to estimate the ORs of GC according to gender (male vs. female), age (45–64 vs. 35–44), baseline histopathological categories (superficial IM; deep IM; mild DYS; IM with glandular atrophy and neck hyperplasia; and moderate or severe DYS; all these compared with SG/CAG as a reference group) and extensiveness of precursor lesions (diagnosis based on more than 3 biopsy sites vs. 1–3 for SG/CAG, more than 2 sites vs. 2 for IM and more than 1 vs. 1 for DYS).

RESULTS

After the exclusion of 13 subjects diagnosed with GC at the baseline survey, 3,386 subjects were followed. In total, 68 died and 12 were lost to follow-up between the spring of 1989 and the fall of 1994. Therefore, 3,306 subjects were considered eligible for examination in 1994. Of these, 557 did not participate in the survey because of sickness (75), refusal (318) or absence from the area (164). Endoscopic examinations were completed on 2,749 persons, with 2,628 subjects having sufficient histo-pathologic diagnoses. Table I shows the gender and age distributions of the subjects who participated in 1989 baseline, those who received 1994 follow-up examinations and those who did not participate in 1994 follow-up examination. Although the mean age of the 557 subjects who did not participate in 1994 examinations was slightly older than that of the 2,628 who did (48.5 ± 8.7 vs. 46.1 ± 8.9 for males and 47.4 ± 8.7 vs. 45.1 ± 8.1 for females) ($p > 0.05$), the baseline gastric pathology was similar between the 2 groups. The distribution of lesions at baseline examination was 37% for SG/mild CAG, 9% for severe CAG, 10% for superficial IM, 26% for deep IM and 19% for DYS among the non-participants vs. 39%, 8%, 10%, 22% and 19%, respectively, among the participants in the 1994 follow-up examination.

Table II shows the distribution of various transitions among the 2,628 subjects during the follow up period, which averaged 4.5 years. Many (68%) subjects with SG/mild CAG at baseline persisted in this state. Of subjects with severe CAG at baseline, 49% had less advanced gastric lesions in 1994, while 42% had more advanced lesions. In contrast, subjects with superficial IM at baseline were more likely to advance (50%) than to regress (37%). An equal percentage of subjects with deep IM at baseline (27%) progressed and reverted to lesser lesions. A large fraction of the subjects with mild DYS at baseline were diagnosed with mild DYS (27%) or deep IM (47%) in 1994; 1.6% progressed to moderate or

TABLE I – NUMBER AND FREQUENCIES (%) OF GENDER AND AGE DISTRIBUTIONS AMONG THE SUBJECTS WHO PARTICIPATED IN BASELINE, PARTICIPATED IN FOLLOW-UP EXAMINATION, AND DID NOT PARTICIPATE IN FOLLOW-UP EXAMINATION

	1989 Baseline		1994 Follow-up		Non-participants in 1994 follow-up	
	Males	Females	Males	Females	Males	Females
Age						
35–39	524 (29.5)	494 (30.6)	428 (31.5)	411 (32.3)	69 (23.4)	66 (25.2)
40–44	370 (20.7)	389 (24.1)	291 (21.4)	326 (25.7)	53 (18.0)	51 (19.5)
45–49	186 (10.5)	197 (12.3)	147 (10.8)	151 (11.9)	30 (10.2)	38 (14.5)
50–54	252 (14.2)	211 (13.1)	185 (13.6)	152 (12.0)	50 (17.0)	46 (17.6)
55–59	249 (14.0)	203 (12.6)	180 (13.3)	160 (12.6)	47 (15.9)	32 (12.2)
60–64	194 (10.9)	117 (7.3)	126 (9.3)	71 (5.6)	46 (15.6)	29 (11.0)
Total	1775	1611	1357	1271	295	262
Mean age	46.7 ± 9.0	45.7 ± 8.3	46.1 ± 8.8	45.1 ± 8.1	48.5 ± 9.1	47.4 ± 8.7

TABLE II – FREQUENCIES (%) OF GASTRIC HISTO-PATHOLOGY FROM THE 1994 FOLLOW-UP EXAMINATION ACCORDING TO 1989 BASELINE HISTO-PATHOLOGICAL STATUS¹

	n	1994 Follow-up pathology							
		SG/mild CAG (n = 1042)	sev CAG (n = 86)	sup IM (n = 235)	deep IM (n = 836)	mild DYS (n = 368)	M or S DYS (n = 27)	GC (n = 34)	
1989 baseline pathology									
SG/mild CAG	1032	67.5	3.8	7.7	15.0	5.5	0.4	0.1	100%
sev CAG	208	49.2	9.1	10.6	22.6	6.7	1.4	0.0	100%
sup IM	256	32.4	4.7	12.5	37.9	11.7	0.0	0.8	100%
deep IM	586	15.9	1.5	10.2	47.6	22.3	1.7	2.7	100%
mild DYS	503	13.0	1.4	7.6	46.9	27.2	1.6	2.8	100%
M or S DYS	43	13.9	0.0	9.3	39.5	25.6	4.7	7.0	100%
	2628								

¹Abbreviations: sev CAG: severe CAG; sup IM: superficial IM; M or S DYS: moderate or severe DYS.

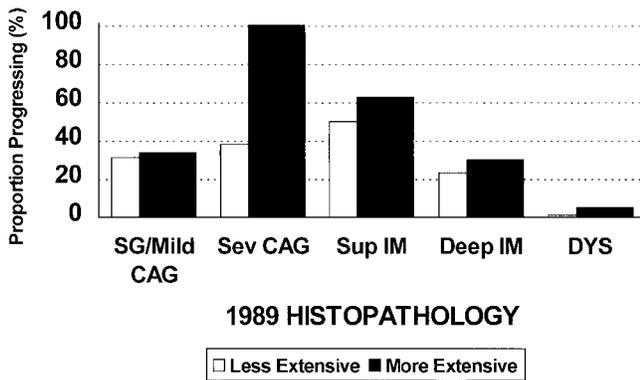


FIGURE 1 – Proportion of subjects progressing to more advanced precancerous gastric lesions in 4.5 years by extensiveness of lesions and 1989 baseline histo-pathology.

severe DYS and 2.8% to GC. Only 4.7% of the subjects with moderate or severe DYS remained in the same stage, while 7.0% progressed to GC. The proportion with progression to more advanced lesions rose steadily, from 33% of the subjects with SG/mild CAG, to 42% of those with severe CAG, and to 50% of those with superficial IM, followed by a decline to 27% of the subjects with deep IM, 4.2% of those with mild DYS and 7.0% of those with moderate or severe DYS.

Figure 1 shows the proportions progressing to more advanced lesions by extensiveness of lesions in each 1989 histo-pathology category. For any given baseline diagnosis, the rates of progression were higher among subjects with more vs. less extensive lesions, particularly for severe CAG (98%).

Table III shows the risks of progression to superficial IM, deep IM or DYS from 3 separate logistic regression models. Compared with SG/mild CAG at baseline, ORs of progression to more advanced gastric lesions increased significantly as baseline pathology status increased. Risks of progression to superficial IM or above were higher for those with severe CAG than SG/mild CAG (OR=1.7, 95% CI, 1.2–2.3). Risks of progression to deep IM or above were higher for those with severe CAG (OR=1.6, 95% CI, 1.1–2.2) or superficial IM (OR=3.7, 95% CI, 2.8–4.9) than for those with SG/mild CAG. Risks of progression to DYS or GC also rose with increasing severity of gastric lesions at baseline (OR=1.4 to 4.7, trend test, $p < 0.001$). Similar results were obtained when age was entered into the logistic models as continuous variables with linear and quadratic components.

During the approximately 4.5 year follow-up, 34 incident GCs were diagnosed (24 men and 10 women); 9 were detected in the second endoscopic examination (1992), 8 became clinically evident prior to the final endoscopic examination (1994) and 17 were

TABLE III – ORs¹ OF PROGRESSION TO ADVANCED PRECANCEROUS GASTRIC LESIONS ACCORDING TO SEX, AGE AND BASELINE HISTO-PATHOLOGY

1989 Baseline	1994 Follow-up progression to					
	sup IM or above		deep IM ² or above		DYS or GC	
	OR	95% CI	OR	95% CI	OR	95% CI
Gender						
Females	1.0	—	1.0	—	1.0	—
Males	1.2	0.9–1.5	1.3	1.0–1.6	1.4	1.1–1.9
Age						
35–44	1.0	—	1.0	—	1.0	—
45–64	1.3	1.0–1.7	1.4	1.1–1.8	1.5	1.2–2.0
Gastric histo-pathology						
SG or mild CAG	1.0	—	1.0	—	1.0	—
sev CAG	1.7	1.2–2.3	1.6	1.1–2.2	1.4	0.8–2.4
sup IM			3.7	2.8–4.9	2.2	1.4–3.4
deep IM					4.7	3.4–6.4

¹SG/mild CAG is used as the reference group (OR = 1.0). Regressions included gender, age group and baseline histo-pathology in a multivariate model. ²Abbreviation: see Table I.

diagnosed during the final examination. Among the 34 GCs diagnoses, 29 (85%) were confirmed by histological review of tissue specimens, while 5 (15%) were based on clinical findings from surgery or endoscopic examinations. Among 34 GC, 23 (67.6%) were early cancers and 5 (15%) were located in the angulus, 20 (59%) in the antrum, 6 (18%) in the body and 3 (9%) in the cardia of the stomach. All cancers with histologically confirmed GC had adenocarcinoma, including 11 well differentiated, 4 moderately differentiated, 13 poorly differentiated and 1 mixed type.

Table IV shows the risks of GC, with age, gender, extensiveness of the gastric lesions and baseline pathology entered into the logistic regression model. Subjects who were 45 years or older had 3 (95% CI, 1.3–7.1) times the risk of GC in younger subjects, while the OR for men vs. women, adjusted for age and histo-pathology, was 1.7 (95% CI, 0.8–3.6). The OR for GC was twice (95% CI, 1.0–4.5) as high among subjects with more vs. less extensive lesions. The ORs varied from 17.4 (95% CI, 1.3–202) for those with superficial IM to 29.3 (95% CI, 3.9–219) for deep IM or IM with glandular atrophy and neck hyperplasia or mild DYS to 104.2 (95% CI, 9.7–999) for moderate or severe DYS (relative to OR=1.0 for SG/CAG). Similar results were obtained after adjustment for age as a continuous variable with linear and quadratic components. In addition, 2 (13.3%) of the 15 subjects with baseline IM without brush borders (incomplete type) developed GC, compared with 16 (1.9%) of the 827 subjects with IM and brush borders (complete type).

DISCUSSION

In an area of China with an exceptionally high mortality from GC, we carried out a large longitudinal study with repeat gastroscopies to evaluate the transition of precancerous gastric lesions in a

TABLE IV – ORs¹ OF GC ACCORDING TO GENDER, AGE, AND EXTENSIVENESS AND TYPES OF BASELINE HISTO-PATHOLOGY

1989 Baseline	1994 Follow-up progression to GC ³	
	OR	95% CI
Gender		
Females	1.0	—
Males	1.7	0.8–3.6
Age		
35–44	1.0	—
45–64	3.1	1.3–7.1
Extensiveness of lesions		
Less extensive lesions	1.0	—
More extensive lesions	2.1	1.0–4.5
Gastric histopathology		
SG or CAG	1.0	—
Sup IM	17.4	1.5–202
Deep IM ²	29.3	3.9–219
M or S DYS	104.2	9.7–999

¹SG/CAG is used as the reference group (OR = 1.0). Regression included gender, age group, extensiveness and baseline histopathology in a multivariate model. ²Deep IM category includes: deep IM, IM with glandular atrophy and neck hyperplasia (elongation of pits reaching to deeper layers of the mucosa and proliferation of foveolar cells) and mild DYS. ³Abbreviations: see Table I.

population affected with a wide range of histo-pathologic lesions at baseline. One strength of our study was the large size and representative nature of the cohort, which was selected by sampling 14 villages at random from Linqu County and including eligible members of the population aged 35–64 years. Another strength was the use of consistent endoscopic and pathologic techniques at baseline and follow-up examinations.

We identified what appear to be 2 main phases in the precancerous process. In the first phase, superficial gastritis is a relatively common inflammatory condition affecting the superficial portion of the lamina propria (You *et al.*, 1993). It is frequently accompanied in this study population by a mild degree of focal glandular loss (atrophy). When the atrophy becomes more extensive and distorts the mucosal architecture, metaplasia appears, first in the superficial layer. Excessive replication is a frequent companion of atrophic gastritis and may be associated with a high rate of progression. This trend, however, may be reversible. Indeed, nearly half of the subjects with severe CAG at baseline had less advanced lesions 4.5 years later, along with 37% of those with superficial IM, thus contributing to a relatively small absolute risk of GC during follow-up (the 4.5-year probabilities of developing GC ranged from 0.1 to 0.8%). In the second phase, IM extends to the deep pepsinogen-secreting portion of the mucosa (deep IM), involving the proliferative compartment, cells replicate excessively (IM with glandular atrophy and neck hyperplasia) and/or the glandular mucosa becomes progressively atypical as it evolves to DYS, with abnormal differentiation and disorganization and an accumulation of genetic alterations (13–17). As a consequence, GC risk increases sharply for these advanced precancerous lesions (4.5-year probabilities of 2.7% for deep IM, 2.8% for mild DYS and 7.0% for moderate or severe DYS, respectively).

IM is widely regarded as precancerous, particularly colonic IM (type III metaplasia or incomplete form) (Filipe *et al.*, 1994; Correa, 1988; Rokkas *et al.*, 1991; Tosi *et al.*, 1993). We did not use mucin histochemistry to distinguish between small intestinal and colonic types of IM in our study. However, results in our study support the concept that individuals with colonic type of IM have a greater risk of developing GC (Filipe *et al.*, 1994; Rokkas *et al.*, 1991; Tosi *et al.*, 1993).

We found the odds of developing GC to be 104 times greater among subjects with moderate or severe DYS at baseline than among those with SG or CAG. The chance that a person with moderate or severe DYS develops GC is estimated to be 7%, compared with 0.1% for a person with SG or CAG. Although based

on only 43 subjects, this finding indicates the need for close monitoring of individuals with advanced lesions. However, among the 546 subjects with DYS at baseline, 92% had mild DYS, and in this group by 1994, 47% had deep IM while only 4% progressed to a more severe lesion, suggesting that mild DYS often remains stable or regresses, as has been noted by others (Rugge *et al.*, 1994; Oehlert *et al.*, 1979; Saraga *et al.*, 1987). Although in some cases, it may be difficult to distinguish epithelial reaction or regeneration lesions from mild DYS (Saraga *et al.*, 1987), medical surveillance is important, particularly for those with persistent diagnoses of DYS or deep IM on repeat biopsies.

For all precancerous lesions, men had a higher rate of progression than women, consistent with the higher prevalence of IM and DYS reported in men at baseline in this population (You *et al.*, 1993), and with the male predominance of GC in Linqu and worldwide (You *et al.*, 1988; Nomura, 1996). The higher rate of progression to more advanced lesions among older than younger subjects is consistent with the results of a study in Colombia (Correa *et al.*, 1990a,b), and with the notion that gastric carcinogenesis is a cumulative multistage process.

It is noteworthy that nearly three fourth of the cases of GC were found in the antrum and the angulus, where the prevalences of IM and DYS are higher (You *et al.*, 1993). This result is consistent with an earlier case-control study of 564 GC cases in Linqu, in which 63% of the tumors were diagnosed in the antrum or angulus (You *et al.*, 1988), an anatomic pattern similar to that reported in a high-risk area of Japan (Yamada and Kato, 1989). The reasons for high rates of progression in the antrum and along the lesser curvature in both Linqu and Japan (Kimura, 1972) are not entirely clear.

Our study also revealed that subjects with more extensive lesions in the same histo-pathologic category (particularly severe CAG) had a higher risk of progression to more advanced states. Age may be related to the extensiveness of the gastric lesions, but fewer than half of those with widespread involvement were 45 years of age or above, and extensiveness acted as an independent predictor of progression in models which adjusted for age.

Sampling errors resulting from an inability to biopsy exactly the same locations in the 2 endoscopic surveys may influence the results of the study (Plummer *et al.*, 1997). DYS tended to be smaller and more dispersed so that sampling variation might occur in repeat biopsies (You *et al.*, 1993a; Correa *et al.*, 1990b). In addition, the accuracy of resampling also depends on the number of biopsy sites; more biopsies yield a greater chance of detecting advanced lesions. Nevertheless, our study showed a clear trend of progression with severity of gastric lesions at the start of follow-up, particularly in the risk of GC.

Causes of precancerous gastric lesions in this region are not fully understood. We reported previously that *H. pylori* infection and cigarette smoking were risk factors for precancerous gastric lesions, and high serum concentrations of vitamin C and beta-carotene, showed a protective effect in the baseline study (You and Chang, 1993).

In summary, our large population-based cohort study in a high-risk area of China has provided data on rates of progression of precancerous gastric lesions and risk of GC among individuals with a spectrum of precancerous gastric lesions at baseline. The study identified high rates of progression from superficial to deep IM and from deep IM to DYS and GC. The findings strongly support the concept that gastric carcinogenesis involves a slow but continuous stepwise evolution from glandular atrophy to metaplasia to dysplasia and, finally, to carcinoma.

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