Precancerous Gastric Lesions in a Population at High Risk of Stomach Cancer

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ABSTRACT

A population-based screening for detection of early cancers evaluated the prevalence of precancerous gastric lesions in an area in Shandong province, China, with one of the world's highest rates of stomach cancer. A total of 3433 residents aged 35 to 64 yr received gastroscopical examinations with biopsies taken from standard locations. Chronic atrophic gastritis was nearly universal; less than 2% of the population had biopsies showing entirely normal mucosa or only superficial gastritis. Intestinal metaplasia was the most advanced lesion for 33% and gastric dysplasia for 20%, although the prevalence of each increased significantly with age. Intestinal metaplasia and gastric dysplasia were detected throughout the stomach, but the lesions were more pronounced along the lesser curvature, especially in the antrum and corpus. There was no sex difference in rates of chronic atrophic gastritis, but males had a slightly higher prevalence of intestinal metaplasia, a 1.6-fold increase in dysplasia, and a 3-fold excess of gastric cancer. The data quantify the extensiveness of gastric lesions likely to be involved in the natural history of stomach cancer in this high-risk population.

INTRODUCTION

Age-adjusted rates of stomach cancer mortality exceeding 70 deaths per year per 100,000 males in Linqu, a rural county in Shandong province in northeast China, are among the highest in China and the world (1, 2). Reasons for the elevated mortality are not clear, although a case-control study of this cancer recently identified several risk factors, including high intake of locally consumed fermented pancakes and low consumption of fresh fruits and vegetables (3). The study also found a 3-fold increase in risk of stomach cancer among subjects with self-reported prior chronic gastritis. CAG and accompanying IM have been implicated in other areas of the world where stomach cancer rates are high, such as Japan and Colombia (4), and may precede the onset of the majority of intestinal-type stomach cancers. As part of a screening program to detect early stomach cancers in Linqu, a population-based investigation of the prevalence of precancerous gastric lesions, their determinants, and rates of transition was launched in 1989. In this paper we describe the distribution and pathological characteristics of the gastric lesions among Linqu residents.

MATERIALS AND METHODS

The screening was carried out in 14 villages selected at random within four townships of Linqu county. After the names of all residents aged 35 to 64 yr were transcribed from the village population rosters, health officials visited each person to explain the study and invite him/her to participate. If an individual was willing to participate, an appointment was made for an examination. All residents were invited except those who were ill or disabled. The reasons for nonparticipation were recorded, but no further attempts were made to enroll those who did not wish to participate.

All participants were given a brief physical examination, and their medical history was recorded. Subjects who had significant blood clotting disorders, high blood pressure, liver disease, or chronic obstructive pulmonary disease were excluded from further examination. The remainder were instructed to fast overnight prior to their visit to the clinic for a gastroscopical examination. The examinations were performed by three experienced gastroenterologists using fiberoptic gastrosopes (Olympus Q20). The gastric mucosa was observed visually by a gastroenterologist, and 7 biopsies were taken from the following standard locations: midway between the cardia and angulus on the lesser curvature; the middle of the greater curvature of the corpus; the center of the angulus along the middle portion of the lesser curvature; 1 cm from the pylorus along the lesser curvature; the posterior wall of the antrum; the anterior wall of the antrum; and the greater curvature of the antrum. In two of the villages, an eighth biopsy was taken within 2 cm of the cardia along the lesser curvature. If severe lesions were visually observed, additional biopsies were taken.

The biopsy specimens were immediately fixed in 10% neutral formalin solution in individually labeled vials. Subsequently, the specimens were embedded and stained with hematoxylin and eosin in the pathology laboratory of the Beijing Institute for Cancer Research where each pathological slide was reviewed by a panel of three senior pathologists. The slides were interpreted according to a protocol proposed by the Chinese Association of Gastric Cancer (5) after review of these procedures by experts in gastric pathology from China and the United States.

The presence or absence of SG, CAG, IM, and DYS was recorded for each biopsy. Each biopsy was given an overall diagnosis based upon the most severe histology, and each subject was assigned a global diagnosis based upon the most severe diagnosis among any of the biopsies. Briefly, the diagnostic criteria for each histological classification are illustrated in Figs. 1 to 5 and described as follows.

Normal. The gastric mucosa is normal histopathologically.

SG. For convenience, all nonatrophic gastritis is 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 not atypical. Polymorphonuclear leukocytes are seen in the lamina propria, pits, and epithelium, indicating chronically active gastritis. SG is subclassified according to two grades: mild (the inflammatory infiltrate is limited to the neck zone) and severe (the inflammatory infiltrate extends deeper into the mucosal layer). The latter grade is sometimes called diffuse antral gastritis.

CAG. Glandular morphology disappears partially or completely in the mucosa replaced by connective tissues. Interglandular spaces are infiltrated mainly by plasma cells and lymphocytes. Sometimes polymorphonuclear leukocytes are seen in the glandular epithelium and lumen, indicating active disease. CAG is classified into three types: I, glandular atrophy with intestinal metaplasia; II, glandular atrophy with hyperplasia of pits; and III, simple glandular atrophy. Each type of CAG is graded as mild or severe depending upon the extent of disappearance of glandular morphology in the mucosa.

IM. Glandular mucosal atrophy is replaced by mucosa resembling that found in the intestines. Goblet cells in tubular glands are the main histological feature. IM is graded as superficial, involving the surface epithelium and pits, or deep, involving the deep pepsinogen-secreting portion of the gastric glands.

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

The population rosters of the 14 villages listed 4382 persons aged 35 to 64 yr. Of these, 237 (5%) were not contacted because of sickness or disability. Among the remainder, 149 (4%) were out of the village, 298 (7%) were not willing to participate in this survey, 241 (6%) had acute illness or were excluded from gastroscopy because of results of their physical examination, and 24 (0.5%) did not participate for other reasons. Endoscopical examinations thus were completed on 3433 persons (83% of those recruited). A total of 33 subjects were later excluded because of insufficient tissue samples. Therefore, 3400 subjects (1792 males, 1608 females) were included in this analysis. Almost 90% of the participants were born in Linqu, and 96% were farmers or housewives.

Among those screened by the gastroscopical examinations, 13 cases of GC were detected: 11 in the antrum (angulus, 4; interior wall, 3; posterior wall, 2; greater curvature, 2) and 2 in the body of the stomach (greater curvature, 1; cardia, 1). Seven of the cases were intestinal type, 4 were diffuse type, and 2 were mixed types. Ten of the cases were male and 3 were female, for prevalence rates of 0.56% and 0.19%, respectively. All but 3 were early stage tumors.

Fig. 6 shows the prevalence rates of SG, CAG, IM, and DYS according to both the global (i.e., most severe) and overall (i.e., presence of these lesions in any biopsy) diagnosis; in total, 3062 (90.1%) subjects had SG, 3335 (98.1%) had CAG, 1795 (52.8%) had IM, and 692 (20.4%) had DYS in at least one biopsy. The numbers with global diagnoses of SG, CAG, IM, or DYS were 57 (1.7%), 1523 (44.8%), 1123 (33.0%), and 683 (20.1%), respectively. These prevalences varied by age, however, as shown in Fig. 7, with a downward trend in CAG and an upward trend for IM and especially DYS. The prevalence of DYS was significantly higher among males than females at nearly all ages with males having a 57% higher prevalence overall (Table 1). There was a 3-fold excess of GC among males.

Most (92%) of the 683 persons with DYS had mild forms, while 52 had moderate or severe DYS, a prevalence rate of 1.5% in this population. Among those with IM, 71% had deep and 29% superficial forms. Among the 1523 persons with a global diagnosis of CAG, 89% had type III, and 11% had type II (persons with type I CAG were all classified as IM).

Fig. 8 presents the frequency distribution of the number of biopsy sites with DYS, IM, or CAG among subjects with a global diagnosis of DYS, IM, or CAG, respectively. For 63% of those with DYS, diagnosis was based on dysplasia appearing in a single biopsy. IM also was most often detected in one or two biopsies, but one third of those with IM had this lesion in three or more biopsies (versus one sixth of those with DYS diagnosed in 3 or more biopsies). In contrast, 84% of the subjects with a global diagnosis of CAG had this lesion in 3 or more biopsy sites.

The prevalence rates of the most severe lesion at each of the 7 standard gastric biopsy sites plus the gastric cardia are given in Table 2. The highest prevalences of DYS were found along the lesser curvature, particularly at the angulus or the antrum where prevalence reached 11% among males and 7% among females. The lowest rates (0 to 2%) of DYS among both men and women were found along the greater curvature of the corpus. The anatomical distribution for IM was generally similar to that of DYS, with highest prevalences (22 to 25%) in the angulus and along the lesser curvature of the antrum and lowest (4 to 8%) along the greater curvature of the corpus. The prevalence of CAG as the most severe lesion in the individual biopsy...
sites ranged from 25 to 60%, again with the highest rates among the biopsies from the antrum and the angulus. Prevalence rates for SG or normal tissue were highest in the greater curvature and lowest in the angulus and antrum. As shown in the table, the percentage distributions across anatomical locations for DYS, IM, CAG, and SG were similar for males and females, although the prevalence rates of both DYS and IM were higher among males than females at nearly every biopsy site.

Persons with a global diagnosis based upon one or more biopsies often had less severe lesions in the same or other biopsies. In the 13 GC patients, 8 (62%) also had DYS, and 5 others had deep IM without DYS. Among the DYS subjects, 640 (94%) also had deep IM, with the remainder affected by superficial IM or CAG. The percentage of persons with DYS having IM coexisting in the same biopsy versus in other biopsies is given in Table 3. IM was very common not only in the same biopsy as the dysplasia (being a concomitant diagnosis in over 90%) but also in other biopsies (75 to 83%). In contrast, among the 2709 persons without DYS, IM was reported in the same biopsy for 41%. Of the subjects with a global diagnosis of IM, 833 (74%) also had glandular atrophy (CAG I) in at least one biopsy, while of the remainder, 164 (15%) had pit hyperplasia (CAG II) and the rest had simple atrophic gastritis (CAG III).

**DISCUSSION**

This large screening survey in an area with exceptionally high rates of stomach cancer revealed a pervasive presence of precancerous gastric lesions. The high prevalences were not due to including only persons with gastrointestinal complaints, because the random sampling procedure and high participation rate resulted in a study group representative of the Linqu population aged 35 to 64 yr. We found that CAG was nearly universal by age 35, so that the onset of the condition must have occurred in most individuals at considerably earlier ages. Nearly 40% of Linqu residents were affected by IM, and about one eighth with concomitant DYS, by the age of 35 to 39 yr, but the prevalence of DYS increased nearly 3-fold by the age of 60 to 64 yr, so that even this advanced lesion was common among older residents.

The prevalence of precancerous gastric lesions in Linqu may be among the highest in the world, although only limited population-based data are available on their occurrence elsewhere. Direct comparisons with Linqu are hindered in part because of variations in diagnostic criteria and perhaps even more because of the differing numbers of biopsy sites evaluated. In an area of Colombia at high risk of stomach cancer, endoscopical surveys using generally similar diagnostic criteria and examining 4 or more biopsies in most persons found that about 75% of the population aged 35 yr and over was...
affected with atrophic gastritis, with IM as the most severe diagnosis for 29% and DYS for 9% (6). The prevalence of the lesions increased significantly with age, but differences by sex were small (6). In Finland, atrophic gastritis was found via single biopsies in 28% of 142 residents in a rural area (7). In Japan among patients undergoing gastroscopy from 1985 to 1989 at the Aichi Cancer Center because of clinical symptoms, IM was detected in over one half and occurred more often in males and at older ages (8). In another survey in Japan among persons undergoing gastroscopy (with 5 biopsies) because of radiological suspicion of GC, IM was found in 80% of males and 40% of females over age 40 (9), but this was a highly selective group not representative of the Japanese population at large. Elsewhere in China, suction biopsies taken from population screenings in 9 provinces

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**Table 1 Age-specific prevalence of gastric cancer and precancerous lesions based on the global (most severe across all biopsies) diagnosis**

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age (yr)</th>
<th>No. of cases</th>
<th>GC</th>
<th>DYS</th>
<th>IM</th>
<th>CAG</th>
<th>SG</th>
</tr>
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<tbody>
<tr>
<td>Male</td>
<td>35-39</td>
<td>523</td>
<td>0.4</td>
<td>17.4</td>
<td>26.0</td>
<td>53.5</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td>40-44</td>
<td>374</td>
<td>0.4</td>
<td>20.3</td>
<td>32.4</td>
<td>45.7</td>
<td>1.6</td>
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<tr>
<td></td>
<td>45-49</td>
<td>192</td>
<td>0.5</td>
<td>21.9</td>
<td>32.8</td>
<td>43.2</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>50-54</td>
<td>256</td>
<td>0.4</td>
<td>29.2</td>
<td>34.6</td>
<td>32.7</td>
<td>2.3</td>
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<tr>
<td></td>
<td>55-59</td>
<td>250</td>
<td>0.8</td>
<td>30.8</td>
<td>40.4</td>
<td>26.4</td>
<td>1.6</td>
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<tr>
<td></td>
<td>60-64</td>
<td>197</td>
<td>2.0</td>
<td>36.5</td>
<td>34.5</td>
<td>26.9</td>
<td>1.8</td>
</tr>
<tr>
<td>Total</td>
<td>1792</td>
<td>0.6</td>
<td>24.1</td>
<td>32.2</td>
<td>41.1</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>35-39</td>
<td>488</td>
<td>9.8</td>
<td>30.1</td>
<td>57.4</td>
<td>2.7</td>
<td></td>
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<tr>
<td></td>
<td>40-44</td>
<td>389</td>
<td>14.4</td>
<td>28.5</td>
<td>55.3</td>
<td>1.8</td>
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<td></td>
<td>45-49</td>
<td>197</td>
<td>10.7</td>
<td>37.6</td>
<td>50.3</td>
<td>0.5</td>
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<tr>
<td></td>
<td>50-54</td>
<td>211</td>
<td>67.0</td>
<td>19.0</td>
<td>43.1</td>
<td>37.4</td>
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<td></td>
<td>55-59</td>
<td>204</td>
<td>24.0</td>
<td>37.3</td>
<td>37.7</td>
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<tr>
<td></td>
<td>60-64</td>
<td>119</td>
<td>30.3</td>
<td>38.7</td>
<td>30.3</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1608</td>
<td>0.2</td>
<td>15.5</td>
<td>33.9</td>
<td>48.9</td>
<td>1.5</td>
<td></td>
</tr>
</tbody>
</table>

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**Fig. 5.** Dysplasia, severe. H & E, X 80.

**Fig. 6.** The prevalence of rates of SG, CAG, IM, and DYS by global (■) and overall (□) diagnosis.

**Fig. 7.** The age-specific prevalence rates of SG, CAG, IM, and DYS by global diagnosis. ■ DYS; □ IM; △ CAG; ■ SG.

**Fig. 8.** Percentage distributions of the number of biopsy sites with CAG, IM, and DYS by global diagnosis.
showed wide variation in the prevalence of gastritis (10). In persons undergoing endoscopy for clinical reasons in the southwestern United States, IM was detected in 25% when 4 biopsies were taken compared to 11% when there were 2 biopsies (11). If we had taken only a single biopsy from the antrum, the data in Tables 1 and 2 indicate that the percentages with dysplasia would have been reduced by more than one half.

Generally speaking, males throughout the world have a higher rate of gastric cancer than females (12). This is true in Linqu also (3). We found CAG to be nearly universal in both sexes. Males, however, had a slightly higher rate of IM in nearly all of the 8 stomach biopsy sites, with the male excess becoming marked for dysplasia, consistent with findings in Japan (9). It is unclear why the male/female differential becomes more pronounced with advancing lesions, although initial results from interviews in Linqu reveal that cigarette smoking contributes to this pattern (13). However, further study is needed to elucidate factors influencing the prevalence and progression of precancerous gastric lesions.

Although we have only cross-sectional data, the patterns by age and sex are consistent with the concept that GC, especially the intestinal type, often arises from a series of mucosal changes involving glandular atrophy, metaplasia, and dysplasia. Among those with GC, concomitant DYS and IM were generally found. Among those with DYS, IM almost always coexisted in the same biopsy, suggesting that DYS was an end result of progression of CAG and IM. IM also was detected in increased frequency in the other biopsies of those with DYS. The DYS seen was typically mild, with only a small proportion of moderate or severe grades. While only a fraction of the mild dysplasias may progress to more advanced forms, it is also possible that the time spent in a dysplastic state is relatively short compared to the time spent in mild DYS, and thus mild DYS is more likely to be detected in our cross-sectional prevalence survey. In addition, persons with IM had CAG, more often the severe types, in the same or other biopsies. Finally, we found the anatomical distributions of DYS, IM, and CAG to be similar, with lesions being more common in the antrum, where we and others have found GC also to be more frequent (4). These features all suggest that the pathogenesis of intestinal GC involves a multistep process, with a slow but continuous evolution from CAG to IM to DYS and, finally, to carcinoma.

In conclusion, this large population-based survey has quantified the extensiveness of precancerous gastric lesions among the general population of an area in China where rates of stomach cancer are exceptionally high. The findings suggest a biological model involving a stepwise progression of precursor states that can be evaluated in further investigations. Now ongoing in Linqu are studies to evaluate a variety of possible determinants of IM and DYS, to prospectively follow up the study population to quantify rates of transition in gastric mucosal status over time and eventually to develop measures to prevent GC, still one of the leading cancers in the world.

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