World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v22.i22.5228

World J Gastroenterol 2016 June 14; 22(22): 5228-5236
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Case Control Study

Factors affecting occurrence of gastric varioliform lesions: A case-control study

Tian-Hui Zou, Ru-Hua Zheng, Qin-Yan Gao, Xuan Kong, Xiao-Yu Chen, Zhi-Zheng Ge, Ying-Xuan Chen, Xiao-Ping Zou, Jing-Yuan Fang

Tian-Hui Zou, Qin-Yan Gao, Xuan Kong, Xiao-Yu Chen, Zhi-Zheng Ge, Ying-Xuan Chen, Jing-Yuan Fang, Division of Gastroenterology and Hepatology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai Institute of Digestive Disease, Shanghai 200001, China

Ru-Hua Zheng, Xiao-Ping Zou, Division of Gastroenterology and Hepatology, the Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing 210008, Jiangsu Province, China

Author contributions: Zou TH performed telephone interviews of most participants and wrote the manuscript; Zheng RH performed part of the telephone interviews; Gao QY and Kong X provided analytical tools; Chen XY offered the pathological data; Ge ZZ offered the endoscopic data; Chen YX served as scientific advisors; Fang JY designed the study and edited the manuscript; all authors approved the final version of the manuscript.

Supported by National Natural Science Foundation of China, No. 31371420 (to FJY); the National Key Technology R and D Program, No. 2014BAI09B05 (to CYX); and the National Natural Science Foundation of China, No. 81402347 (to KX).

Institutional review board statement: The study was approved by Shanghai Jiao Tong University School of Medicine.

Informed consent statement: All patients gave informed consent.

Conflict-of-interest statement: No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

Data sharing statement: Statistical code and dataset available from the corresponding author at jingyuanfang@sjtu.edu.cn.

Correspondence to: Jing-Yuan Fang, PhD, Division of Gastroenterology and Hepatology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai Institute of Digestive Disease, No. 145 Shandong Zhonglu, Shanghai 200001, China. jingyuanfang@sjtu.edu.cn
Telephone: +86-21-63200874
Fax: +86-21-63266027

Received: January 18, 2016
Peer-review started: January 19, 2016
First decision: March 7, 2016
Revised: March 16, 2016
Accepted: March 30, 2016
Article in press: March 30, 2016
Published online: June 14, 2016

Abstract

AIM: To investigate the factors influencing the occurrence of gastric varioliform lesions (GVLs) and their possible link with gastric cancer.

METHODS: A 1:1 matched case-control study was performed to retrospectively analyze data from 1638 chronic gastritis patients who had undergone gastroscopy at one of two Chinese hospitals between 2009 and 2014. Patients with GVLs (cases) were compared to those without such lesions (controls). Endoscopic and pathological findings were recorded, along with interview information on *Helicobacter pylori* (*H. pylori*) infection, medical, drug and family histories, lifestyle and eating habits. The association between each factor and the occurrence of GVLs was estimated, and then multivariate conditional logistic regression was used to evaluate the independent factors.

RESULTS: The frequency and severity of glandular

atrophy, intestinal metaplasia (IM) and low-grade intraepithelial neoplasia were significantly increased in the GVL group ($P < 0.01$). Overall analysis showed that *H. pylori* infection [3.051 (2.157, 4.317), $P < 0.001$], allergic respiratory diseases [3.636 (2.183, 6.055), $P < 0.001$], work-related stress [2.019 (1.568, 2.600), $P < 0.001$], irregular meals [2.300 (1.462, 3.619), $P < 0.001$], high intake of spicy food [1.754 (1.227, 2.507), $P = 0.002$] and high intake of fresh fruit [0.231 (0.101, 0.529), $P = 0.001$] were significantly correlated with the occurrence of GVLs (positively, except for the latter). Stratified analyses indicated that pickled food consumption in patients over 50 years old [7.224 (2.360, 22.115), $P = 0.001$] and excessive smoking in men [2.013 (1.282, 3.163), $P = 0.002$] were also positively correlated, and that, for antral GVLs, vegetable consumption [0.491 (0.311, 0.776), $P = 0.002$] was negatively correlated.

CONCLUSION: Seven risk factors and two protective factors are determined for GVLs, which were found to be associated with premalignant abnormalities.

Key words: Gastric cancer; Gastric varioliform lesions; Precancerous lesion; Risk factor; Varioliform gastritis

Core tip: To our knowledge, this is the first case-control study investigating the factors influencing the formation of gastric varioliform lesions, which were supposed to be associated with gastric neoplasia in previous reports. Our results indicate a potentially increased cancer risk for the affected patients, and that *Helicobacter pylori* infection, allergic respiratory diseases, high work-related stress, irregular meals, high intake of spicy food, pickled food consumption in elder people, excessive smoking in men, consumption of vegetables and high intake of fresh fruit are found to be correlated with the occurrence of gastric varioliform lesions.

Zou TH, Zheng RH, Gao QY, Kong X, Chen XY, Ge ZZ, Chen YX, Zou XP, Fang JY. Factors affecting occurrence of gastric varioliform lesions: A case-control study. *World J Gastroenterol* 2016; 22(22): 5228-5236 Available from: URL: http://www.wjgnet.com/1007-9327/full/v22/i22/5228.htm DOI: http://dx.doi.org/10.3748/wjg.v22.i22.5228

INTRODUCTION

Varioliform gastritis (VG), or "octopus sucker" gastritis in the foreign literature and verrucous gastritis in the national literature, is a disease with a characteristic endoscopic manifestation but no specific clinical symptoms. The major endoscopic feature is the presence of gastric varioliform lesions (GVLs), namely, widespread small lesions, manifesting as round, oval or irregularly shaped elevations, often possessing a central umbilical-like depression covered in gray-colored secretion or tiny bleeds. In 1947, Moutier and Martin[1] first described two cases of this distinctive gastric mucosal disease, and then in 1978, Lambert *et al*[2] classified the disease, according to its site of occurrence, into "diffuse" VG when spread throughout the stomach, and "antral" VG when restricted to the antrum. These two forms of VG are thought to have different etiopathogenesis and histological manifestations[3]. VG has been recognized as a protruded type of chronic erosive gastritis in the Consensus on Chronic Gastritis in China (2012)[4], but endoscopists more often present the diagnosis as chronic gastritis with varioliform lesions.

Until recently, very little was known about the etiopathogenesis of GVLs. Malfertheiner *et al*[5] reported that the *Helicobacter pylori* (*H. pylori*) infection rate was 89% among 37 patients with GVLs, and their clinical symptoms and mucosal inflammation were substantially improved after effective eradication of the infection. In the national literature, most authors support this point of view and regard *H. pylori* as the main cause of GVLs. On the other hand, several studies have provided compelling evidence that type Ⅰ hypersensitivity may play a role[6]. Andre *et al*[7] found a large number of IgE-containing cells in the affected gastric mucosa and a significantly increased incidence of allergic diseases in patients with GVLs, as compared with the normal population. Furthermore, they performed a randomized double-blind placebo-controlled trial to compare clinical and endoscopic outcomes in patients treated with sodium cromoglycate, cimetidine or placebo[8]. The result stated that treatment with sodium cromoglycate greatly improved both sets of outcomes, whereas treatment with cimetidine or placebo showed no appreciable effect. Other previously reported pathogenic factors include hyperacid[9] and viral infection[10].

Some reports suggest a possible association between GVLs and gastric neoplasia. In 1960, Munoz Monteavaro *et al*[11] observed "*in situ*" carcinomatous transformation in a patient with VG, and other groups have reported similar findings more recently[12,13]. The elevated lesions can persist and transform into sessile polyps and appear as a gastric carcinoma several years later; as a result, the disease was classified as a precursor to gastric cancer at the World Congress of Gastroenterology (WCOG) in 1994. Diverse risk factors are involved in gastric carcinogenesis, including bacterial, environmental, dietary and genetic variables[14]. Numerous epidemiological studies have attempted to shed light on the factors impacting gastric neoplasia and precancerous lesions; these include a history of diabetes[15], aspirin consumption[16], excessive smoking[17] and drinking[18], pickled food consumption[19], tea consumption[20], amongst others. However, the results are somewhat inconsistent due

to the ethnic diversity and limited sample size. A recent systematic review concluded that smoking, drinking, red meat and pickled food were risk factors, and that fresh vegetables and fruit may be protective; there was insufficient evidence to draw conclusions regarding coffee, tea or seafood[21]. GVLs may share some of these risk factors, and clarifying the matter should provide a better understanding of this potentially premalignant condition, allowing physicians to better identify at-risk patients and to devise more effective treatment strategies. Therefore, we carried out a retrospective 1:1 matched bi-center case-control study, analyzing endoscopic and pathological data from 1638 patients with chronic gastritis. The association between potentially relevant variables and the occurrence of GVLs was systematically evaluated, with an aim to find independent risk factors and protective factors.

MATERIALS AND METHODS

Study sample and selection criteria

A 1:1 matched case-control study was conducted, analyzing data from outpatients who had undergone gastroscopy at Renji Hospital, Shanghai Jiao-Tong University School of Medicine or the Nanjing Drum Tower Hospital, Nanjing University School of Medicine between 2009 and 2014. A total of 1638 chronic gastritis patients were enrolled, all of which fell into one of two categories: those with GVLs (cases; n = 819) or those without such lesions (controls; n = 819).

To populate the case group, we searched the electronic databases of the aforementioned hospital endoscopic centers, using the following keywords: "varioliform gastritis" or "with gastric varioliform lesions" or "with erosive elevations"; then we closely examined the corresponding patient images and selected those patients having at least three typical lesions. Any disagreement was discussed by T.H. Zou and R.H. Zheng before reaching a consensus. Control patients, who were diagnosed with chronic gastritis at the same time, but without varioliform lesions, were matched one by one with the case group members, based on gender, age ± 2 years, month of examination and endoscopist. The exclusion criteria were strictly adhered to and were as follows: those who had no biopsy, those who were diagnosed with gastric cancer and those who had undergone partial or total gastrectomy. For those who had repeated examinations, we only recorded data from the first diagnostic gastroscopy.

Data extraction

The endoscopic and pathological findings were recorded. All the patients were required to undergo a gastroscopy with biopsies for the diagnosis. All parts of the upper gastrointestinal tract were carefully examined for any lesions by experienced endoscopists, and at least two biopsies were taken from the antrum. If suspected lesions were found, 2 to 5 more biopsies were taken. Pathological examinations for chronic gastritis were made by experienced pathologists according to the visual analogue scale (VAS) in the updated Sydney System[22,23] that is associated with the Consensus on Chronic Gastritis in China. Histological diagnosis of intraepithelial neoplasia was made based on the World Health Organization (WHO) classification[24]. To concretely differentiate the severity of inflammation, glandular atrophy or IM in the present study, a scheme was introduced using the following calculation: grading index = $(S_1 \times B_1 + S_2 \times B_2 + \ldots + S_n \times B_n)/B_n$, where S is the severity of a particular biopsy specimen, B is the number of the relevant specimen and n is the quantity of specimens[25].

H. pylori infection was detected using a *H. pylori* rapid urease test during endoscopic examination, HE and Giemsa staining of biopsy specimens, and a ^{13}C urea breath test. We defined a positive result as meeting one of the following two criteria: (1) the rapid urease test or HE staining was positive; or (2) if both urease and HE results were negative, yet the specimen was highly inflamed, Giemsa staining was added or a ^{13}C urea breath test was performed, and a positive outcome was considered indication of *H. pylori* infection. A ^{13}C urea breath test was subsequently used when evaluating the effect of eradication on *H. pylori* infection.

A questionnaire was designed by the authors and it was used to conduct telephone interviews with all patients in the study. The investigators were trained to be polite and methodical during interviews and they avoided calling patients at working, or otherwise busy hours. The questionnaire requested information on the patient's gender, age, *H. pylori* infection history, medical history, allergic diseases, drug history, family history, long-term lifestyle and eating habits. *H. pylori* infection history was categorized according to four different conditions: currently infected, but with no previous history of infection; chronic (repeated or persistent) infection; past infection that has been completely eradicated; no current or past infection. Allergic diseases consisted of bronchial asthma, allergic rhinitis, allergic skin disease, drug allergy, *etc*. The presence of allergic diseases was mainly based on the interview data, and the authors made the judgment with reference to the guideline of diagnosis for each disease. Lifestyle variables included sleep quality, work-related stress, tobacco smoking and alcohol consumption. Eating habits comprised irregular meals, intake of spicy food, pickled food, fried food, fresh fruit and vegetables; consumption of a particular food type over four time per week was considered high.

Statistical analysis

Statistical analyses were performed using SPSS Version 20.0 (SPSS Inc., Chicago, IL, United States).

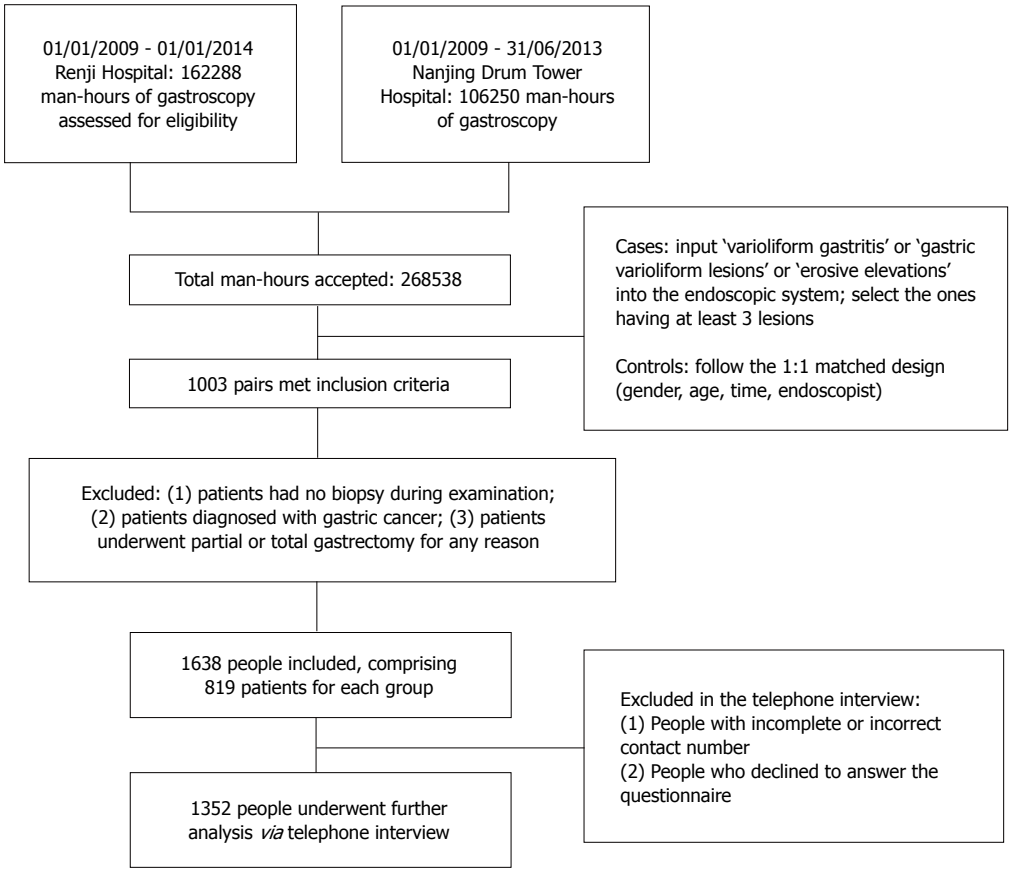

Figure 1 Flow chart of participant selection in the case-control study.

Table 1 Characteristics of the case group *n* (%)

Characteristic	
In total	819 (100)
Hospital	
Renji	491 (60.0)
Drum tower	328 (40.0)
Age (yr)	
< 50	278 (33.9)
⩾ 50, < 60	289 (35.3)
⩾ 60	252 (30.8)
Gender	
Men	448 (54.7)
Women	371 (45.3)
Illness part	
Antral form	806 (98.4)
Diffuse form	13 (1.6)
H. pylori infection	
H. pylori (+)	263 (32.1)
H. pylori (-)	556 (67.9)
Histology	
Glandular atrophy	363 (44.3)
IM	265 (32.4)
Intraepithelial neoplasia	92 (11.2)

H. pylori: *Helicobacter pylori*.

Measurement data were compared between the two groups using a paired *t*-test; where appropriate, numerical data were subjected to a chi-square test, while categorical data using a Mann-Whitney test. Single-factor analysis was used to estimate the association between each potential factor and GVLs, and then multivariate conditional Logistic regression analysis was applied to determine the independent risk and protective factors. Odds ratios (ORs) with 95% confidence intervals (95%CIs) were used to assess the magnitude of the associations. A two-sided *P*-value < 0.05 was considered statistically significant.

RESULTS

The systematic database search yielded 268538 man-hours of gastroscopy over the five-year period of interest. Following the inclusion/exclusion criteria and the 1:1 matched design, 1638 subjects were selected to populate the case and control groups. A flow chart of the selection process is presented in Figure 1. There were 448 men and 371 women in the case group, with a mean age of 53.40 ± 11.41 years (ranging from 18 to 87 years old). The basic, endoscopic and pathological characteristics of the case group are shown in Table 1.

Analysis of histological data

We compared the frequencies of *H. pylori* infection, glandular atrophy, IM and intraepithelial neoplasia between the cases and controls using a χ^2 test. The difference was significant for *H. pylori* infection (OR

Table 2 Overall and stratified analyses of histological data in the case-control study

	Case	Control	OR [95%CI]	*P*-value
Overall analysis				
H. pylori (+)	263	141	2.275 [1.801, 2.872]	< 0.001[b]
Glandular atrophy	363	271	1.610 [1.317, 1.967]	< 0.001[b]
IM	265	182	1.674 [1.343, 2.087]	< 0.001[b]
Intraepithelial neoplasia	92	65	1.468 [1.052, 2.049]	0.023[a]
Antral form				
H. pylori (+)	254	139	2.208 [1.745, 2.794]	< 0.001[b]
Glandular atrophy	341	268	1.472 [1.202, 1.803]	< 0.001[b]
IM	409	179	3.609 [2.908, 4.479]	< 0.001[b]
Intraepithelial neoplasia	79	65	1.239 [0.878, 1.747]	0.222
Diffuse form				
H. pylori (+)	9	2	12.375 [1.828, 83.767]	0.015[a]
Glandular atrophy	13	3		< 0.001
IM	11	3		0.005
Intraepithelial neoplasia	12	0	18.333 [2.522, 133.26]	< 0.001[b]

[a]$P < 0.05$; [b]$P < 0.01$, the case group *vs* the control group. *H. pylori*: *Helicobacter pylori*.

= 2.275, 95%CI: 1.801-2.872, $P < 0.01$), especially in the patients with diffuse GVLs. We also noted statistically significant findings in the pooled analysis for the association between glandular atrophy, with or without IM, and the formation of such lesions. Furthermore, a significantly increased risk of low-grade intraepithelial neoplasia was observed in the case group (OR = 1.468, 95%CI: 1.052-2.049, P = 0.023); this is known to be a premalignant condition. When the patients were further stratified according to VG form, the differences between patients with antral lesions and their matched controls were significant for glandular atrophy and IM, but not for intraepithelial neoplasia. On the other hand, diffuse lesions were strongly associated with all these histological parameters, including intraepithelial neoplasia. The results of the overall and stratified analyses are presented in Table 2.

Indices for grading inflammation, glandular atrophy and IM were calculated separately for the GVL patients and their matched controls. Paired *t*-tests showed that all these indices were significantly increased in the case group ($P < 0.01$).

Analysis of telephone interview data

For 49 patients, the contact number was incomplete or incorrect, and 94 declined to answer the questionnaire. Thus, there was a total of 1352 participants, comprising 676 people from each group; the answering ratio was 82.5%. Single-factor analyses of potential factors demonstrated that current infection with *H. pylori* (OR = 2.203), chronic infection with *H. pylori* (OR = 2.493), bronchial asthma (OR = 6.837), allergic rhinitis (OR = 2.963), family history of gastric cancer (OR = 1.926), high work-related stress (OR = 1.871), irregular meals (OR = 1.703), and high intake of spicy food (OR = 1.540) were positively associated with the occurrence of GVLs, while high intake of fresh fruit was negatively associated (OR = 0.721).

We found a negative correlation between current and chronic infection with *H. pylori* (Pearson coefficient, -0.113), and a positive correlation between bronchial asthma and allergic rhinitis (Pearson coefficient, 0.151). No correlation was found for any other factors. For subsequent analyses, we combined current and chronic infection into a single "*H. pylori* infection" category, and asthma and rhinitis were combined into "allergic respiratory diseases". Based on the results of single-factor analyses, we included the factors with a *P*-value less than 0.05 into the multivariate conditional Logistic regression equation. The adjusted analysis suggested that *H. pylori* infection, allergic respiratory diseases, high work-related stress, irregular meals and high intake of spicy food were independent risk factors for the formation of GVLs; and that high intake of fresh fruit was an independent protective factor. Table 3 shows the overall results of the single-factor and multivariate analyses.

Stratified analysis of telephone interview data

The participants were stratified by age, gender and VG form, and the results of the subsequent analysis are shown in Table 4. For those under 50 years old, high intake of fried food was significantly more common in the GVL group (P = 0.038) under univariate analysis; however, the correlation was not significant in the final multivariate analysis, suggesting that fried food intake may be a confounding factor. In those $\geqslant$ 50 years old, univariate and multivariate analyses indicated that pickled food consumption was a new independent risk factor for GVLs. In males, excessive smoking was also found to be a new independent risk factor, while in females, allergic skin diseases seemed to be a confounding factor. For antral form, single-factor analyses showed significant differences between cases and controls for fried food consumption and intake of vegetable side dishes, but only the latter factor was confirmed as an independent factor by the adjusted multivariate analysis. For diffuse form, current or chronic *H. pylori* infection was found in more than half

Table 3 Overall single-factor and multivariate analyses of impact factors in the case-control study

Impact factor	Univariate analysis			Multivariate analysis		
	OR	95%CI	*P*-value	OR	95%CI	*P*-value
H. pylori infection	2.329	[1.802, 3.011]	< 0.001[b]	3.051	[2.157, 4.317]	< 0.001[b]
Allergic Res. Dis.	3.745	[2.365, 5.930]	< 0.001[b]	3.636	[2.183, 6.055]	< 0.001[b]
Family history of GC	1.926	[1.059, 3.503]	0.029[a]	1.628	[0.801, 3.309]	0.178
Stress ↑	1.871	[1.344, 2.603]	< 0.001[b]	2.019	[1.568, 2.600]	< 0.001[b]
Irregular meals	1.703	[1.184, 2.449]	0.004[b]	2.300	[1.462, 3.619]	< 0.001[b]
Spicy food ↑	1.540	[1.156, 2.052]	0.003[b]	1.754	[1.227, 2.507]	0.002[b]
Fresh fruit ↑	0.721	[0.533, 0.974]	0.033[a]	0.231	[0.101, 0.529]	0.001[b]

[a]$P < 0.05$; [b]$P < 0.01$, the case group *vs* the control group. *H. pylori*: *Helicobacter pylori*.

of the affected patients, whereas only two matched controls had ever been infected. The diffuse form seemed to be more highly correlated with *H. pylori* infection, but with only thirteen pairs of participants making up the sample, no more than a general tendency could be assessed. Allergic respiratory diseases and a family history of gastric cancer were more frequent in patients with diffuse varioliform lesions *vs* matched controls.

DISCUSSION

As is widely accepted, intestinal-type gastric carcinogenesis is a multi-stage process, developing from chronic gastritis through a series of precancerous abnormalities to gastric carcinoma[26,27]. In addition, *H. pylori* infection is thought to be the key promoter[28,29]. These precursor conditions include chronic atrophic gastritis with or without IM, with a reported malignancy rate of 0.5%-1%[30,31], and intraepithelial neoplasia[32], which is classified from low to high grade according to WHO specifications. It is reported that 0%-15% of low-grade intraepithelial neoplasia could progress to high-grade, which has an extremely high malignancy rate of 25%-85%[33]. In the present study, the frequency and severity of glandular atrophy, IM and low-grade intraepithelial neoplasia were significantly elevated in the case group, indicating that the presence of GVLs is a potential risk factor for cancer. Nevertheless, no high-grade intraepithelial neoplasia was observed, and the results were inconsistent when analysis was restricted to antral varioliform lesions. Thus, this malignancy risk should be further investigated *via* a large-scale prospective study.

In view of the association between GVLs and *H. pylori* infection status, the literature is somewhat inconclusive[34]. Our analysis showed a statistically significant difference in infection rates between GVL patients (32.1%) and controls (17.2%). The adjusted analysis of the interview data indicated that *H. pylori* infection, especially chronic persistent infection, was a pathogenic factor. In contrast, no correlation existed where infections had been successfully treated. Thus, *H. pylori* eradication and regular endoscopic follow-ups should be key components of the treatment for GVLs.

European researchers have suggested that there may be an allergic component in the pathogenesis of the disease, specifically that excessive histamine release could play a central role[7,35]; however, no evidence for this has been reported for Chinese patients. Interestingly, we found that the frequency of allergic diseases was increased in patients with varioliform lesions, in particular bronchial asthma and allergic rhinitis. There were 112 GVL patients (16.6%) with at least one allergic disease, and the multivariate analysis confirmed that allergic respiratory disease was an independent risk factor. Family history of gastric carcinoma has been reported as a risk factor for gastric carcinogenesis[36,37], but it was not associated with GVLs in our study. Diffuse form appeared to have a more positive association with allergic diseases and family history of gastric cancer, yet the results were not conclusive owing to the limited sample size, and will thus need to be verified by larger studies in the future.

In the pooled multivariate analysis, the independent risk factors were high work-related stress, irregular meals, and high intake of spicy food, and the one potentially protective factor was high intake of fresh fruit. The stratified analyses indicated that pickled food consumption in people over 50 years old and excessive smoking in men were also risk factors. Intake of vegetable side dishes was found to be negatively correlated with the antral form of GVLs. Indeed, certain habits of daily life could serve as important risk factors for gastric cancer. Previous studies revealed a close association between negative psychological factors like nervousness or anxiety and susceptibility to neoplasia[38,39]. Our participants with high work-related stress could have an increased risk of gastric malignancy, which may be related to constant anxiety-induced stimulation of the sympathetic system. Smoking is also considered a pathogenic factor for multiple cancers. A 50-year observational study of 34439 British doctors indicated that cigarette smoking was a risk factor in the progression of 14 different cancers including gastric carcinoma[40]. In the present study, excessive smoking in men contributed significantly to the risk of GVLs, but not in women, indicating possible male predominance in the morbidity

Table 4 Stratified single-factor and multivariate analyses of impact factors in the case-control study

Factor	Case	Control	Univariate analysis		Multivariate analysis	
			OR [95%CI]	*P*-value	OR [95%CI]	*P*-value
Age < 50 yr						
H. pylori infection	69	37	2.224 [1.419, 3.487]	< 0.001[b]	1.968 [1.222, 3.170]	0.005[b]
Allergic Res. Dis.	34	11	3.445 [1.700, 6.978]	< 0.001[b]	3.784 [1.715, 8.347]	0.001[b]
Stress ↑	41	24	1.858 [1.083, 3.189]	0.023[a]	1.452 [1.076, 1.960]	0.015[a]
Irregular meals	40	25	1.723 [1.008, 2.946]	0.045[a]	2.207 [1.112, 4.381]	0.024[a]
Fried food ↑	56	38	1.622 [1.025, 2.567]	0.038[a]	1.459 [0.846, 2.517]	0.174
Spicy food ↑	50	33	1.654 [1.021, 2.681]	0.040[a]	1.838 [1.011, 3.342]	0.046[a]
Age ≥ 50 yr						
H. pylori infection	151	79	2.386 [1.745, 3.263]	< 0.001[b]	3.402 [2.149, 5.386]	< 0.001[b]
Allergic Res. Dis.	51	14	3.988 [2.173, 7.319]	< 0.001[b]	4.894 [2.164, 11.069]	< 0.001[b]
Stress ↑	68	39	1.879 [1.237, 2.855]	0.003[b]	2.265 [1.594, 3.219]	< 0.001[b]
Irregular meals	44	27	1.699 [1.032, 2.798]	0.035[a]	1.680 [0.918, 3.074]	0.092
Picked-food cons.	149	122	1.334 [1.001, 1.778]	0.049[a]	7.224 [2.360, 22.115]	0.001[b]
Spicy food ↑	86	62	1.481 [1.036, 2.117]	0.031[a]	1.786 [1.114, 2.863]	0.016[a]
Fresh fruit ↑	387	405	0.637 [0.409, 0.993]	0.045[a]	0.422 [0.178, 1.001]	0.050
Male						
H. pylori infection	116	67	2.054 [1.458, 2.893]	< 0.001[b]	3.445 [2.114, 5.612]	< 0.001[b]
Allergic Res. Dis.	42	10	4.599 [2.272, 9.310]	< 0.001[b]	6.563 [2.832, 15.209]	< 0.001[b]
Smoking	99	76	1.410 [1.003, 1.981]	0.047[a]	2.013 [1.282, 3.163]	0.002[b]
Stress ↑	63	34	2.023 [1.298, 3.154]	0.002[b]	2.096 [1.489, 2.950]	< 0.001[b]
Irregular meals	52	34	1.614 [1.021, 2.551]	0.039[a]	2.201 [1.262, 3.839]	0.005[b]
Spicy food ↑	79	57	1.488 [1.022, 2.165]	0.037[a]	2.167 [1.285, 3.653]	0.004[b]
Female						
H. pylori infection	104	49	2.727 [1.850, 4.021]	< 0.001[b]	3.031 [1.897, 4.844]	< 0.001[b]
Allergic Res. Dis.	43	15	3.183 [1.726, 5.867]	< 0.001[b]	3.502 [1.691, 7.255]	0.001[b]
Allergic skin Dis.	15	5	3.106 [1.114, 8.660]	0.023[a]	3.223 [0.966, 10.748]	0.057
Stress ↑	46	29	1.694 [1.032, 2.780]	0.036[a]	1.873 [1.356, 2.589]	< 0.001[b]
Irregular meals	32	18	1.872 [1.026, 3.415]	0.039[a]	2.027 [0.905, 4.538]	0.086
Spicy food ↑	57	38	1.619 [1.036, 2.530]	0.033[a]	2.185 [1.236, 3.861]	0.007[b]
Antral form						
H. pylori infection	211	114	2.248 [1.734, 2.914]	< 0.001[b]	3.124 [2.192, 4.452]	< 0.001[b]
Allergic Res. Dis.	80	25	3.552 [2.237, 5.639]	< 0.001[b]	3.432 [2.062, 5.712]	< 0.001[b]
Stress ↑	107	63	1.833 [1.315, 2.554]	< 0.001[b]	1.984 [1.544, 2.550]	< 0.001[b]
Irregular meals	83	52	1.681 [1.168, 2.422]	0.005[b]	2.191 [1.407, 3.412]	0.001[b]
Fried food cons.	202	169	1.281 [1.007, 1.629]	0.044[a]	1.338 [0.955, 1.876]	0.091
Spicy food ↑	133	95	1.500 [1.124, 2.002]	0.006[b]	1.705 [1.188, 2.447]	0.004[b]
Vegetable Cons.	227	262	0.797 [0.637, 0.996]	0.046[a]	0.491 [0.311, 0.776]	0.002[b]

[a]$P < 0.05$; [b]$P < 0.01$, the case group *vs* the control group. *H. pylori*: *Helicobacter pylori*.

of the disease. Concerning food consumption, pickled foods have been associated with the development of esophageal and gastric cancers, which can damage gastric mucosa and exacerbate the inflammation caused by *H. pylori*[41]. In recent times, Chinese dietary habits have changed dramatically. Pickled food may now be less popular in younger sections of the population, whereas spicy foods have greatly increased in popularity. Although capsaicin in spicy food has been shown to help counter the growth of *H. pylori*[42], we found that high intake of spicy food was a risk factor for varioliform lesions. The reason could be related to oncogene exposure or a chemical process during production. Meanwhile, the present study also provided factors that potentially offer some protection against GVLs. Intake of fresh vegetables and fruit has been reported to beneficial for avoidance of gastric neoplasia[43], which is consistent with the corresponding reduction in the frequency of GVLs seen in our study.

Several limitations of the present study must be taken into account. First, it is a retrospective analysis, for which recall bias and selection bias cannot be completely removed; a prospective study would be required to establish a convincing causal relationship between the factors and the disease. Second, the conclusions of the stratified analyses may be of limited value because of the small sample size, especially in the diffuse form group. Thus, some of the results in our study should be interpreted cautiously. Third, other relevant variables such as body mass index (BMI), hyperlipidemia, ABO blood group, consumption of coffee, carbonated drinks and bean products were not included; in addition, several factors such as the type of cigarette or alcohol consumed, medication dose and professional mental scale were not precisely classified. If the above factors were included in the multivariate regression equation, our results could have been very different. Future studies should therefore use a more complete set of variables.

To the best of our knowledge, this is the first case-control study investigating the factors influencing the formation of GVLs. The results suggest a potentially increased cancer risk for the affected patients, and that *H. pylori* infection, allergic respiratory diseases, high work-related stress, irregular meals, high intake of spicy food, pickled food consumption in older people, and excessive smoking in men were all positively correlated with the occurrence of GVLs. In contrast, consumption of vegetables and high intake of fresh fruit were found to be negatively correlated and therefore potentially protective. In summary, our results suggest that formation of GVLs can be reduced by maintaining a healthy lifestyle and positive attitude, while ensuring that allergic diseases and *H. pylori* infection are treated effectively. We suggest that a prospective study should be carried out in the future to examine the morphological and pathological evolution of GVLs, and thereby clarify their relationship with gastric malignancy. A large-scale, well-designed clinical trial is also warranted to provide more precise and robust conclusions on this matter.

COMMENTS

Background

Researchers discovered the presence of gastric varioliform lesions (GVLs) over 60 years ago, but until now, very little was known about the etiopathogenesis and progression. So the authors try to provide a better understanding of this potentially premalignant disease in the present case-control study.

Research frontiers

Previous reports suggested a possible association between GVLs and gastric cancer. And the disease was classified as a precursor to gastric cancer at the World Congress of Gastroenterology in 1994. More recently, Zhang *et al* performed a proteomic analysis to provide more molecular biological details of GVLs. The important differential proteins could serve as potential biomarkers for the early diagnosis of gastric cancer.

Innovations and breakthroughs

This is the first case-control study investigating the factors influencing the formation of GVLs, and the manuscript provide a better understanding of this potentially premalignant condition, allowing physicians to better identify at-risk patients and to devise more effective treatment strategies.

Applications

A large-scale, well-designed prospective study should be carried out in the future to examine the morphological and pathological evolution of GVLs, and thereby clarify their relationship with gastric malignancy.

Terminology

The term GVLs in the present study is a synonym of varioliform gastritis. The major endoscopic feature of such lesions is widespread small lesions, possessing a central umbilical-like depression covered in gray-colored secretion or tiny bleeds. Patients in China are affected more often by the antral type of the disease, thus endoscopists present the diagnosis as GVLs.

Peer-review

Patients diagnosed in an early stage of gastric cancer present an excellent prognosis, with a five-year survival rate greater than 90%. This well conducted and written retrospective case-control study considers the different risk and protective factors influencing the occurrence of GVLs and their possible link with development of gastric cancer.

REFERENCES

1 **Moutier F**, Martin J. [Deux cas de gastrite varioliforme]. *Arch Mal Appar Dig Mal Nutr* 1947; **36**: 155-160 [PMID: 20259201]
2 **Lambert R**, André C, Moulinier B, Bugnon B. Diffuse varioliform gastritis. *Digestion* 1978; **17**: 159-167 [PMID: 414953]
3 **Haot J**, Jouret A, Willette M, Gossuin A, Mainguet P. Lymphocytic gastritis--prospective study of its relationship with varioliform gastritis. *Gut* 1990; **31**: 282-285 [PMID: 2323590]
4 **Fang JY**, Liu WZ, Shi Y, Ge ZZ, Xiao SD. Consensus on chronic gastritis in China--Second National Consensus Meeting on Chronic Gastritis (14-16 September 2006 Shanghai, China). *J Dig Dis* 2007; **8**: 107-119 [PMID: 17532824 DOI: 10.1111/j.1443-9573.2007.00295.x]
5 **Malfertheiner P**, Stanescu A, Baczako K, Bode G, Ditschuneit H. Chronic erosive gastritis--a therapeutic approach with bismuth. *Scand J Gastroenterol Suppl* 1988; **142**: 87-92 [PMID: 3166538]
6 **Monaci M**, Borrelli D. [On the subject of varioliform gastritis with special reference to its allergic character and its relation to gastric ulcer]. *Arch De Vecchi Anat Patol* 1960; **33**: 647-670 [PMID: 13771939]
7 **Andre C**, Moulinier B, Andre F, Daniere S. Evidence for anaphylactic reactions in peptic ulcer and varioliform gastritis. *Ann Allergy* 1983; **51**: 325-328 [PMID: 6349431]
8 **André C**, Gillon J, Moulinier B, Martin A, Fargier MC. Randomised placebo-controlled double-blind trial of two dosages of sodium cromoglycate in treatment of varioliform gastritis: comparison with cimetidine. *Gut* 1982; **23**: 348-352 [PMID: 6804311]
9 **Murata I**, Yoshikawa I, Kuroda T, Tabaru A, Miura T, Otsuki M. Varioliform gastritis and duodenitis associated with protein-losing gastroenteropathy, treated with omeprazole. *J Gastroenterol* 1996; **31**: 109-113 [PMID: 8808438]
10 **Zhang L**, Hou YH, Wu K, Zhai JS, Lin N. Proteomic analysis reveals molecular biological details in varioliform gastritis without Helicobacter pylori infection. *World J Gastroenterol* 2010; **16**: 3664-3673 [PMID: 20677338 DOI: 10.3748/wjg.v16.i29.3664]
11 **Munoz Monteavaro C**, Mendoza D, Palma E. [Varioliform gastritis with "in situ" carcinomatous transformation]. *An Fac Med Univ Repub Montev Urug* 1960; **45**: 72-77 [PMID: 14425269]
12 **Cappell MS**, Green PH, Marboe C. Neoplasia in chronic erosive (varioliform) gastritis. *Dig Dis Sci* 1988; **33**: 1035-1039 [PMID: 3391073]
13 **Gallina F**, Benedetti-Valentini F. [Varioliform gastritis associated with gastric ulcer simulating a neoplasm]. *Riv Gastroenterol* 1963; **15**: 85-94 [PMID: 14133465]
14 **Zou TH**, Wang ZH, Fang JY. Positive association between Toll-like receptor 4 gene +896A/G polymorphism and susceptibility to gastric carcinogenesis: a meta-analysis. *Tumour Biol* 2013; **34**: 2441-2450 [PMID: 23592020 DOI: 10.1007/s13277-013-0795-y]
15 **Xu CX**, Zhu HH, Zhu YM. Diabetes and cancer: Associations, mechanisms, and implications for medical practice. *World J Diabetes* 2014; **5**: 372-380 [PMID: 24936258 DOI: 10.4239/wjd.v5.i3.372]
16 **Tian W**, Zhao Y, Liu S, Li X. Meta-analysis on the relationship between nonsteroidal anti-inflammatory drug use and gastric cancer. *Eur J Cancer Prev* 2010; **19**: 288-298 [PMID: 20386312 DOI: 10.1097/CEJ.0b013e328339648c]
17 **La Torre G**, Chiaradia G, Gianfagna F, De Lauretis A, Boccia S, Mannocci A, Ricciardi W. Smoking status and gastric cancer risk: an updated meta-analysis of case-control studies published in the past ten years. *Tumori* 2009; **95**: 13-22 [PMID: 19366050]
18 **Jarl J**, Heckley G, Brummer J, Gerdtham UG. Time characteristics of the effect of alcohol cessation on the risk of stomach cancer--a meta-analysis. *BMC Public Health* 2013; **13**: 600 [PMID: 23786883 DOI: 10.1186/1471-2458-13-600]
19 **D'Elia L**, Rossi G, Ippolito R, Cappuccio FP, Strazzullo P. Habitual salt intake and risk of gastric cancer: a meta-analysis of prospective studies. *Clin Nutr* 2012; **31**: 489-498 [PMID:

22296873 DOI: 10.1016/j.clnu.2012.01.003]
20 **Yu F**, Jin Z, Jiang H, Xiang C, Tang J, Li T, He J. Tea consumption and the risk of five major cancers: a dose-response meta-analysis of prospective studies. *BMC Cancer* 2014; **14**: 197 [PMID: 24636229 DOI: 10.1186/1471-2407-14-197]
21 **Lee YY**, Derakhshan MH. Environmental and lifestyle risk factors of gastric cancer. *Arch Iran Med* 2013; **16**: 358-365 [PMID: 23725070]
22 **Dixon MF**, Genta RM, Yardley JH, Correa P. Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994. *Am J Surg Pathol* 1996; **20**: 1161-1181 [PMID: 8827022]
23 **Sipponen P**, Price AB. The Sydney System for classification of gastritis 20 years ago. *J Gastroenterol Hepatol* 2011; **26** Suppl 1: 31-34 [PMID: 21199511 DOI: 10.1111/j.1440-1746.2010.06536.x]
24 **Endo S**, Dousei T, Yoshikawa Y, Hatanaka N, Taniyama K, Yamauchi A, Kamiike W, Nishijima J. Gastric neuroendocrine tumors in our institutions according to the WHO 2010 classification. *Int Surg* 2012; **97**: 335-339 [PMID: 23294075 DOI: 10.9738/CC134.1]
25 **Chooi EY**, Chen HM, Miao Q, Weng YR, Chen XY, Ge ZZ, Xiao SD, Fang JY. Chronic atrophic gastritis is a progressive disease: analysis of medical reports from Shanghai (1985-2009). *Singapore Med J* 2012; **53**: 318-324 [PMID: 22584971]
26 **Correa P**. A human model of gastric carcinogenesis. *Cancer Res* 1988; **48**: 3554-3560 [PMID: 3288329]
27 **Correa P**, Haenszel W, Cuello C, Tannenbaum S, Archer M. A model for gastric cancer epidemiology. *Lancet* 1975; **2**: 58-60 [PMID: 49653]
28 **Wong BC**, Zhang L, Ma JL, Pan KF, Li JY, Shen L, Liu WD, Feng GS, Zhang XD, Li J, Lu AP, Xia HH, Lam S, You WC. Effects of selective COX-2 inhibitor and Helicobacter pylori eradication on precancerous gastric lesions. *Gut* 2012; **61**: 812-818 [PMID: 21917649 DOI: 10.1136/gutjnl-2011-300154]
29 **Uemura N**, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, Taniyama K, Sasaki N, Schlemper RJ. Helicobacter pylori infection and the development of gastric cancer. *N Engl J Med* 2001; **345**: 784-789 [PMID: 11556297 DOI: 10.1056/NEJMoa001999]
30 **de Vries AC**, van Grieken NC, Looman CW, Casparie MK, de Vries E, Meijer GA, Kuipers EJ. Gastric cancer risk in patients with premalignant gastric lesions: a nationwide cohort study in the Netherlands. *Gastroenterology* 2008; **134**: 945-952 [PMID: 18395075 DOI: 10.1053/j.gastro.2008.01.071]
31 **den Hoed CM**, Holster IL, Capelle LG, de Vries AC, den Hartog B, Ter Borg F, Biermann K, Kuipers EJ. Follow-up of premalignant lesions in patients at risk for progression to gastric cancer. *Endoscopy* 2013; **45**: 249-256 [PMID: 23533073 DOI: 10.1055/s-0032-1326379]
32 **Won CS**, Cho MY, Kim HS, Kim HJ, Suk KT, Kim MY, Kim JW, Baik SK, Kwon SO. Upgrade of Lesions Initially Diagnosed as Low-Grade Gastric Dysplasia upon Forceps Biopsy Following Endoscopic Resection. *Gut Liver* 2011; **5**: 187-193 [PMID: 21814599 DOI: 10.5009/gnl.2011.5.2.187]
33 **Park SY**, Jeon SW, Jung MK, Cho CM, Tak WY, Kweon YO, Kim SK, Choi YH. Long-term follow-up study of gastric intraepithelial neoplasias: progression from low-grade dysplasia to invasive carcinoma. *Eur J Gastroenterol Hepatol* 2008; **20**: 966-970 [PMID: 18787462 DOI: 10.1097/MEG.0b013e3283013d58]
34 **Kato T**, Yagi N, Kamada T, Shimbo T, Watanabe H, Ida K. Diagnosis of Helicobacter pylori infection in gastric mucosa by endoscopic features: a multicenter prospective study. *Dig Endosc* 2013; **25**: 508-518 [PMID: 23369058 DOI: 10.1111/den.12031]
35 **Caporali R**, Luciano S. Diffuse varioliform gastritis. *Arch Dis Child* 1986; **61**: 405-407 [PMID: 3085599]
36 **Kelley JR**, Duggan JM. Gastric cancer epidemiology and risk factors. *J Clin Epidemiol* 2003; **56**: 1-9 [PMID: 12589864]
37 **Peddanna N**, Holt S, Verma RS. Genetics of gastric cancer. *Anticancer Res* 1995; **15**: 2055-2064 [PMID: 8572602]
38 **Huiping C**, Kristjansdottir S, Bergthorsson JT, Jonasson JG, Magnusson J, Egilsson V, Ingvarsson S. High frequency of LOH, MSI and abnormal expression of FHIT in gastric cancer. *Eur J Cancer* 2002; **38**: 728-735 [PMID: 11916557]
39 **González CA**, Pera G, Agudo A, Palli D, Krogh V, Vineis P, Tumino R, Panico S, Berglund G, Simán H, Nyrén O, Agren A, Martinez C, Dorronsoro M, Barricarte A, Tormo MJ, Quiros JR, Allen N, Bingham S, Day N, Miller A, Nagel G, Boeing H, Overvad K, Tjonneland A, Bueno-De-Mesquita HB, Boshuizen HC, Peeters P, Numans M, Clavel-Chapelon F, Helen I, Agapitos E, Lund E, Fahey M, Saracci R, Kaaks R, Riboli E. Smoking and the risk of gastric cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). *Int J Cancer* 2003; **107**: 629-634 [PMID: 14520702 DOI: 10.1002/ijc.11426]
40 **Doll R**, Peto R, Boreham J, Sutherland I. Mortality from cancer in relation to smoking: 50 years observations on British doctors. *Br J Cancer* 2005; **92**: 426-429 [PMID: 15668706 DOI: 10.1038/sj.bjc.6602359]
41 **Wang XQ**, Terry PD, Yan H. Review of salt consumption and stomach cancer risk: epidemiological and biological evidence. *World J Gastroenterol* 2009; **15**: 2204-2213 [PMID: 19437559 DOI: 10.3748/wjg.15.2204]
42 **Jones NL**, Shabib S, Sherman PM. Capsaicin as an inhibitor of the growth of the gastric pathogen Helicobacter pylori. *FEMS Microbiol Lett* 1997; **146**: 223-227 [PMID: 9011042]
43 **Jenab M**, Riboli E, Ferrari P, Sabate J, Slimani N, Norat T, Friesen M, Tjønneland A, Olsen A, Overvad K, Boutron-Ruault MC, Clavel-Chapelon F, Touvier M, Boeing H, Schulz M, Linseisen J, Nagel G, Trichopoulou A, Naska A, Oikonomou E, Krogh V, Panico S, Masala G, Sacerdote C, Tumino R, Peeters PH, Numans ME, Bueno-de-Mesquita HB, Büchner FL, Lund E, Pera G, Sanchez CN, Sánchez MJ, Arriola L, Barricarte A, Quirós JR, Hallmans G, Stenling R, Berglund G, Bingham S, Khaw KT, Key T, Allen N, Carneiro F, Mahlke U, Del Giudice G, Palli D, Kaaks R, Gonzalez CA. Plasma and dietary vitamin C levels and risk of gastric cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST). *Carcinogenesis* 2006; **27**: 2250-2257 [PMID: 16774936 DOI: 10.1093/carcin/bgl096]

P- Reviewer: Tanimoto MA, Vorobjova T **S- Editor**: Ma YJ
L- Editor: Wang TQ **E- Editor**: Zhang DN

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327
9 771007 932045 22>