

Evaluation of routine biopsies in endoscopic screening for esophagogastric junction cancer

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incidence spot of esophagogastric junction (EGJ) cancer are justified in endoscopic screening.

METHODS: This was a multicenter population-based study conducted in eight high-risk areas in China. A total of 37396 participants underwent endoscopic examination. Biopsies were obtained from visible mucosal abnormalities or from normal-appearing mucosa at the high incidence spot of esophagogastric junction cancer when no abnormality was detected. Specimens showing high-grade intraepithelial neoplasia (HIN) or higher grade lesions were deemed as pathologically "positive". The ratios of positive pathologic diagnosis between participants with abnormal and normal-appearing mucosa were compared using the Pearson χ^2 test. Odds ratios and 95% confidence intervals, adjusted for potential confounders, were calculated using logistic regression.

RESULTS: A total of 37520 individuals participated in this study and 37396 (99.7%) participants had full information and were suitable for analysis. During endoscopic examinations, 9.11% (3405/37396) participants were found to have visible mucosal lesions. Of the participants who had normal-appearing mucosa at the EGJ, only 0.28% (94/33991) were diagnosed with HIN or higher grade lesions, whereas 6.05% (206/3405) of participants with abnormalities at the EGJ had a positive pathologic result. After controlling for other variables, visible abnormal mucosa detected under endoscopy strongly predicted a positive pathologic result (OR = 32.51, 95%CI: 23.96-44.09). The proportion of participants with "positive" pathologic diagnoses increased as the total number of endoscopic examinations performed by the doctors increased (< 5000 cases vs 5000-10000 cases vs > 10000 cases, $Z = -2.7207$, $P = 0.0065$, Cochran Armiger trend test). The same trend was found between the proportion of participants with positive pathologic diagnoses and the total number of years the doctors performed endoscopy (< 5 years vs 5-10 years vs > 10 years, $Z = -10.3222$, $P < 0.001$,

Abstract

AIM: To explore whether routine biopsies at the high

Cochran Armiger trend test).

CONCLUSION: Additional routine biopsies from the high incidence spot of EGJ cancer are of limited value and are unjustified.

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Key words: Esophagogastric junction cancer; High incidence spot; Screening; Endoscopy; Biopsy

Core tip: Our findings offer population-level evidence for the high incidence spot of esophagogastric junction (EGJ) cancer. It is also the first study to evaluate whether the findings at the high incidence spot could be used in endoscopic screening in high-risk populations to increase the detection rate. We found that visible mucosal abnormalities of the EGJ at endoscopy were strongly associated with pathologic diagnoses of high-grade intraepithelial neoplasia or higher grade lesions. When no abnormalities were detected, routine biopsies from normal-appearing mucosa at the high incidence spot in endoscopic screening were unjustified in high-risk populations.

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INTRODUCTION

In the past two decades, studies from Western countries^[1,2], China^[3], Iran^[4] and Japan^[5] have all reported an increasing incidence of cancers arising from the esophagogastric junction (EGJ). In China, cancer registry data from 1998 to 2002 showed that the world age-standardized incidence rates of EGJ cancers for males were 46.7/10⁵, 82.8/10⁵, 40.8/10⁵ and 89.1/10⁵ in Cixian, Yangcheng, Linzhou and Shexian, respectively^[6], making it the third most common malignancy in these regions. Recently, an asymmetrical circumferential distribution of EGJ cancers has been described in Chinese patients. Wang *et al*^[7] found that over 75% of EGJ cancers were located at the right anterior side of the EGJ at endoscopy, specifically at the most proximal gastric rugae of the lesser curvature. Subsequent observations indicated that 91%-95% of early stage EGJ cancers and precancerous lesions originated from this specific site^[8-10]. Thus, this circumferential asymmetry in the formation of pathological lesions at the EGJ led to the identification of the high incidence spot of junctional lesions in China. Similar findings of such an asymmetrical circumferential distribu-

tion of lesions at the EGJ have also been found in Iran^[4] and Japan^[11,12] where a high incidence of upper gastrointestinal cancers (UGIC) have been reported. These findings were adopted by the Chinese Ministry of Health's cancer screening guidelines (2005), named The Practice of Screening, Early Diagnosis and Early Treatment for Esophageal and Cardiac Cancer. The preliminary version of the guidelines recommended endoscopists take multiple biopsies from visible abnormal mucosa at the EGJ at endoscopy or a routine biopsy at the high incidence spot of EGJ when no mucosal abnormality was detected^[13].

However, the additional routine biopsy at the high incidence spot of the EGJ remains controversial among doctors conducting these screening programs in high-risk populations. Several recent investigations have shown that 90% of EGJ cancers could be detected *via* mucosal abnormalities at endoscopy, including congestion, roughness, erosion, and nodularity^[14,15], and have suggested that contrary to the current guidelines, biopsies should only be taken from visible gross lesions at the EGJ, thereby avoiding excessive biopsies. However, other studies have pointed out that a significant proportion of early stage EGJ adenocarcinomas were diagnosed from biopsies of asymptomatic mucosa *via* endoscopy^[16]. In addition, it was observed that 5% of normal-appearing and pathologically-confirmed healthy mucosa progressed to EGJ cancers in a high-risk Chinese population taking part in a 15-year prospective study^[17]. Moreover, the detection of endoscopically recognizable lesions usually requires examination by highly skilled and experienced endoscopists, whereas village doctors conducting these screening projects are typically from community-based hospitals in rural China and have only received basic medical training. In order to reduce the missed diagnoses among these endoscopists, they continued to use the first version of the guidelines given that additional routine biopsy played a crucial role in the early detection of EGJ cancers. These inconsistent findings were mainly from hospital-based studies that were limited in sample size or restricted to only one high-risk area in China. To provide more population-based evidence to determine whether additional routine biopsies at the high incidence spot of EGJ cancer are necessary, we performed a population-based study in eight high-risk areas for upper gastrointestinal tract cancers in China.

MATERIALS AND METHODS

Study design and participants

This was a multicenter population-based, cross-sectional study conducted in eight counties with a high incidence of upper gastrointestinal tract cancers, namely Linzhou, Cixian, Shexian, Feicheng, Yangzhong, Taixing, Yangcheng and Yanting. Based on previous field studies and population registry data, each county has 10-20 villages. The target population (aged 38-72 years) accounted for approximately 25% of total residents in each county.

The number of villages (two to five, respectively)

selected was based on the health resources and research capacity of each county. One study investigator visited the local health facility in each village to notify them of the impending study and arranged a date to drive the participants to the hospitals. Eligible participants were healthy locals, who were aged 38 to 72 years without contraindications for endoscopic examinations (*e.g.*, severe cardiovascular or respiratory disease). Participants with a history of upper gastrointestinal surgeries, liver cirrhosis, esophageal varices, hematemesis, severe bleeding diathesis, unstable angina, psychiatric diseases or allergy to lidocaine were excluded. All eligible subjects in each village were invited to participate. In total, 27 villages were selected and over 70% of eligible residents from these villages participated in our study and signed a voluntary written informed consent document at the time of entry into the study.

All phases of this study were approved by the Institutional Review Board of the Cancer Foundation of China.

Endoscopic examination

All endoscopic examinations were conducted in eight local cancer hospitals, respectively, using the following procedure: after signing the informed consent, participants were anesthetized with 5 mL 1% lidocaine per os for 5 min. Participants were then placed in the left lateral position. The entire esophagus and stomach were examined, but only the EGJ was analyzed. The EGJ was recognized as the most proximal extent of the gastric fold at endoscopy. Tumors with an epicenter lying at the EGJ, or within 1 cm proximally and distally were defined as EGJ cancers. During examination, suspicious lesions showing congestion, bleeding, roughness, erosion, plaque and nodularity were targeted and 3-4 endoscopic biopsies were taken. If no mucosal abnormality was detected, 1-2 additional routine biopsies were obtained from the high incidence spot, which is at the right side of the EGJ from the axial view, specifically at the most proximal gastric rugae of the lesser curvature. Visual endoscopic manifestations of the EGJ mucosa were recorded as “normal-appearing” and “abnormal”. All endoscopic examinations were performed by board-certified endoscopists trained by the Cancer Institute/Cancer Hospital, Chinese Academy of Medical Sciences. The skill and experience of the endoscopists were measured by the total number of endoscopic examinations performed (< 5000 cases; 5000-10000 cases; > 10000 cases) and the total number of years performing endoscopy (< 5 years; 5-10 years; > 10 years). Twenty four endoscopists were involved in this study. All endoscopic examinations were performed using the same type of endoscope (Olympus GIF-H260).

Pathologic diagnosis

Biopsy specimens were fixed in 10% buffered formalin, embedded in paraffin, cut into 5 μ m sections, and stained with hematoxylin and eosin. Each biopsy slide was read by two unified-trained local pathologists (16 in total) without knowledge of the visual endoscopic find-

ings, and pathologic diagnoses were made according to the definitions in the World Health Organization (WHO) Classification of Tumours Pathology and Genetics Tumours of the Digestive System (2000). Findings with clinical implications, specifically high-grade intraepithelial neoplasia (HIN) or higher grade lesions were deemed as pathologically “positive” in our study. These patients were offered endoscopic mucosal resection or surgery, depending on the pathological grade. Other participants, including those with low-grade intraepithelial neoplasia (LIN), were regarded as pathologically “negative”. Different follow-up schemes were provided to participants according to their pathologic diagnoses.

Statistical analysis

All analyses were performed using SAS 9.2 (SAS Institute Inc, Cary NC, United States). $P \leq 0.05$ was considered statistically significant. Proportions of diagnoses between participants with abnormal and normal-appearing mucosa were compared using the Pearson χ^2 test. Evidence for associations between pathologic diagnoses and the total number of endoscopic examinations performed by endoscopists and years of performing endoscopy were further assessed using the Cochran Armiger trend test. Univariate binary logistic regression was performed to choose variables that may be associated with the presence of “positive” pathology diagnosis. These variables were: age (continuous), gender (dichotomous), county (eight categories), endoscopic manifestations (dichotomous), total number of endoscopic examinations performed by a given endoscopist (three categories) and total number of years performing endoscopy (three categories). Variables showing a significant association ($P \leq 0.05$) were further analyzed using multivariate logistic regression.

RESULTS

From 2006 to 2008, a total of 37520 individuals participated in this study and 37396 (99.7%) participants had full information and were suitable for analysis. The mean age of the 37396 participants was 51.52 ± 7.92 years. During endoscopic examinations, 9.11% (3405/37396) of participants were found to have visible mucosal lesions. Endoscopic records also showed the percentages of participants with abnormal mucosa by individual county, which ranged from 1.00% (Yangting, 59/5911) to 33.96% (Feicheng, 1016/2992). Pathologic results indicated that there were 300 positive cases, 144 of which came from Linzhou. As shown in Table 1, Linzhou also had the largest proportion of total participants (18.08%, 6763/37396), while only 8.02% (2999/37396) were from Yangcheng.

Table 2 shows the frequency distribution in terms of different pathologic and endoscopic results. Among participants who had normal-appearing mucosa at the EGJ, only 0.28% (94/33991) were diagnosed with HIN or higher grade lesions, whereas 6.05% (206/3405) of participants with abnormalities at the EGJ had a positive

Table 1 Distribution of demographic characteristics, pathology and endoscopy results by county *n* (%)

County	Median age (range, yr)	Gender		Endoscopy		Pathology		Total
		Male	Female	Normal	Abnormal	Positive	Negative	
Linzhou	51 (32)	2876 (42.53)	3887 (57.47)	6159 (91.07)	604 (8.93)	144 (2.13)	6619 (97.87)	6763 (18.08)
Cixian	50 (33)	3004 (46.47)	3461 (53.53)	5512 (85.26)	953 (14.74)	45 (0.70)	6420 (99.30)	6465 (17.29)
Shexian	50 (32)	1933 (45.82)	2286 (54.18)	3588 (85.04)	631 (14.96)	7 (0.17)	4212 (99.83)	4219 (11.28)
Feicheng	52 (32)	1552 (51.87)	1440 (48.13)	1976 (66.04)	1016 (33.96)	30 (1.00)	2962 (99.00)	2992 (8.00)
Yangzhong	49 (34)	2367 (49.59)	2406 (50.41)	4721 (98.91)	52 (1.09)	41 (0.86)	4732 (99.14)	4773 (12.76)
Taixing	52 (34)	1345 (41.08)	1929 (58.92)	3219 (98.32)	55 (1.68)	20 (0.61)	3254 (99.39)	3274 (8.75)
Yangcheng	51 (34)	1521 (50.72)	1478 (49.28)	2964 (98.83)	35 (1.17)	3 (0.10)	2996 (99.90)	2999 (8.02)
Yanting	53 (29)	3118 (52.75)	2793 (47.25)	5852 (99.00)	59 (1.00)	10 (0.17)	5901 (99.83)	5911 (15.81)
Total	51 (34)	17716 (47.37)	19680 (52.63)	33991 (90.89)	3405 (9.11)	300 (0.80)	37096 (99.20)	37396 (100.00)

Table 2 Distribution of pathologic diagnoses by mucosa manifestation, total number of endoscopies performed and number of years performing endoscopy *n* (%)

Distribution	Pathology		Total	<i>P</i> value
	Positive	Negative		
Mucosa manifestation (at endoscopy)				< 0.001 ¹
Abnormal	206 (6.05)	3199 (93.95)	3405	
Normal	94 (0.28)	33897 (99.72)	33991	
Total number of endoscopies performed				0.0065 ¹
< 5000	46 (0.55)	8275 (99.45)	8321	
5000-10000	19 (0.92)	2053 (99.08)	2072	
> 10000	235 (0.87)	26768 (99.13)	27003	
Years of performing endoscopy				< 0.001 ¹
< 5	11 (0.18)	6009 (99.82)	6020	
5-10	86 (0.50)	16952 (99.50)	17038	
> 10	203 (1.42)	14135 (98.58)	14338	

¹Statistically significant (*P* < 0.05).

pathologic result. This difference was significant by Pearson's χ^2 test ($\chi^2 = 1296$, *P* < 0.001).

Overall, 72% (27003) of endoscopies in this study were conducted by senior endoscopists who had performed more than 10000 endoscopic examinations and 83.9% of the doctors had practiced endoscopy for more than 5 years. A statistically significant trend between pathologic diagnoses and total number of endoscopies performed by a given endoscopist was found. The proportion of participants with "positive" pathologic diagnoses increased as the total number of endoscopic examinations performed increased (< 5000 cases *vs* 5000-10000 cases *vs* > 10000 cases, *Z* = -2.7207, *P* = 0.0065, Cochran Armiger trend test). The same trend was found between the proportion of participants with positive pathologic diagnoses and the total number of years the doctor had performed endoscopy (< 5 years *vs* 5-10 years *vs* > 10 years, *Z* = -10.3222, *P* < 0.001, Cochran Armiger trend test). Biopsies taken by more experienced or skilled endoscopists had a higher proportion of positive pathologic diagnoses.

Univariate logistic regression analysis demonstrated significant associations (*P* ≤ 0.05) between positive pathologic diagnoses and six variables, respectively: age, gender, county, endoscopic manifestations, the total number of endoscopic examinations performed by a given

endoscopist and his/her total number of years performing endoscopy. Thus, these six variables were all included in the subsequent multivariate logistic regression model. Using a stepwise approach (SLE = 0.05, SLS = 0.05), age, gender, county, endoscopy manifestations and the total number of endoscopic examinations performed by a given endoscopist were significantly associated with a positive pathologic diagnosis in the final multivariable model (Table 3). After controlling for other variables, visible abnormal mucosa detected at endoscopy strongly predicted a positive pathologic result (OR = 32.51, 95%CI: 23.96-44.09).

DISCUSSION

In China, government-sponsored screening projects for seven cancers have been initiated in high-risk areas since 2005, namely cancers of the cervix, esophagus, colorectum, liver, nasopharynx, stomach and breast. The technical support unit of these projects, the Cancer Foundation of China, established the committee of experts and developed the preliminary version of screening guidelines for each cancer. These preliminary versions were largely based on limited clinical studies and experience from cancer screening programs in other countries. However, most of the recommendations lacked solid evidence from large Chinese populations. Therefore, revisions based on evidence from research and clinical practice in China is of great importance. The aim of our study was to clarify the existing controversy among doctors regarding the use of routine biopsy of the high incidence spot of the EGJ using population-level data.

The findings from our study suggest that routine biopsies from the high incidence spot of EGJ cancers are of limited value and are unjustified. Taking biopsies from the 3405 participants with visible abnormal mucosa at endoscopy enabled the detection of 6.05% (206/3405) of patients with HIN or higher grade lesions at the EGJ. When adjusted for potential confounders, a strong association between visible mucosal abnormality and positive pathologic result was also observed in the multivariate analysis. Compared with participants who showed normal-appearing mucosa at endoscopy, the risk of HIN or higher grade lesions was 32 times higher in patients with visible lesions at the EGJ. In contrast, routine biopsies of

Table 3 Multivariate logistic regression analysis: Independent variables and corresponding odds ratios for positive pathologic diagnosis

Selected variables	<i>b</i>	OR	OR, 95%CI	<i>P</i> value
Age (yr)	0.08	1.09	1.07, 1.10	< 0.0001 ¹
Gender				
Male	0.42	2.32	1.75, 3.06	< 0.0001 ¹
Female	0.00	1.00		
County				
Linzhou	0.00	1.00		
Cixian	-0.39	0.20		0.0508
Shexian	-1.76	0.05	0.02, 0.11	< 0.0001 ¹
Feicheng	-0.72	0.14	0.09, 0.22	0.0004 ¹
Yangzhong	2.03	2.19	1.27, 3.76	< 0.0001 ¹
Taixing	0.66	0.56	0.33, 0.93	0.0069 ¹
Yangcheng	-0.55	0.17		0.3177
Yanting	-0.51	0.17		0.0975
Endoscopy				
Abnormal	1.74	32.51	23.96, 44.09	< 0.0001 ¹
Normal	0.00	1.00		
Total number of endoscopies performed				
< 5000	-0.47	0.45	0.22, 0.91	0.0110 ¹
5000-10000	0.00	1.00		
> 10000	0.13	0.81		0.3014

¹Statistically significant (*P* < 0.05).

33991 patients with normal-appearing mucosa only identified 94 additional pathologically positive cases (0.28%). Thus, following the original guidelines unnecessarily exposed 33897 (90.6% of the total population) participants to the risks of biopsy, compared with taking biopsies only from those with visibly abnormal mucosa. Furthermore, a diagnostic biopsy for high risk areas of upper gastrointestinal carcinomas (UGIC) typically costs 100 Yuan (approximately \$16.0) before taking into account medical resources; therefore the cost of 33897 excess biopsies is considerable.

Although 31.33% (94/300) of the patients with pathologically positive biopsies in this study were identified *via* routine biopsy of the high incidence spot of the EGJ, this finding should be interpreted carefully. Results from several prospective studies have suggested that precancerous lesions, such as HIN were reversible^[18,19]. Therefore, the actual number of patients who may have developed clinically significant junctional cancers is likely to be less than 94, this regression of premalignant lesions may be attributed to treatment such as *Helicobacter pylori* (*H. pylori*) eradication given the positive association between EGJ cancers and *H. pylori* infection in the Chinese population^[20,21]. Further research is needed to elucidate the mechanisms of this regression using a globally consistent diagnostic criterion. In lieu of performing biopsies in participants with normal-appearing mucosa as previously recommended, a more plausible approach for identifying the additional cases missed by traditional endoscopy would be the development of alternative screening strategies to detect patients at risk of EGJ cancers. Ideally, endoscopy should be performed in individuals found to be positive in a filter selection test.

Given the strength of evidence from our study, the Chinese Expert Committee of Early Detection and Early Treatment of Cancer accepted our unpublished findings and promptly revised the recommendation for routine biopsy at the high incidence spot in 2011. At this time, patients undergoing endoscopic screening for EGJ cancers have biopsies taken only in the setting of visible mucosal lesions^[22]. In order to reduce the percentages of missed diagnoses, an additional retroflex view of EGJ mucosa is now recommended when screening for junctional cancers at endoscopy. Following the straight view examination, the additional retroflexion may increase the chances of doctors detecting visible mucosal lesions, especially when the endoscopists are less skilled or experienced. The procedure is easily performed without causing additional complications and is well tolerated by patients. Based on limited feedback from doctors performing endoscopy according to the revised guidelines, the EGJ is easier to identify and mucosal abnormalities of the EGJ are clearer and more apparent when utilizing the retroflex maneuver. In fact, since adopting the revised guidelines, no obvious decrease in the detection rate has been reported by endoscopists from these high-risk regions. Further studies are needed to provide more population-level evidence on the revised guidelines for screening EGJ cancers.

The eight study sites chosen were formerly known as high-risk areas of esophageal squamous cell carcinoma (OSCC), but recent studies have found that EGJ cancers and distal gastric carcinomas are increasingly prevalent and the clustering of UGIC was observed in all of these regions^[6]. For instance, Cancer registry data from 2009 showed that the age-standardized incidence of gastric cancer and esophageal cancer was 198.55 and 111.99 per 100000 for men and 69.50 and 53.61 per 100000 for women, respectively, in Shexian^[23]. Cancers of the EGJ are still classified as gastric cardia cancer (GCC) in the cancer registry and accounted for over 50% of new cases of gastric cancer in four high-risk areas of UGIC, namely Cixian, Shexian, Linzhou and Feicheng, from 2006 to 2008^[24]. Our results showed that 0.802% of the target population had HIN or higher-grade lesions, which is consistent with previous reports regarding high EGJ cancer prevalence among these high-risk areas.

Despite the consistent findings of a remarkably high and rapidly rising incidence of junctional cancers, the etiology of cancer at this site varies geographically. In most Western countries, junctional cancers are strongly associated with esophagogastric reflux and intestinal metaplasia^[25-27]. Nevertheless, other studies, mainly from Eastern countries, demonstrated a significant association between EGJ cancers and *H. pylori*-induced atrophic gastritis, which is more similar to distal gastric cancer^[20,21,28-30]. Thus, some gastroenterologists postulated that cancers of the esophagus-gastric junction may have two distinct etiologies, with some resembling esophageal adenocarcinomas and others resembling non-cardia gastric cancers^[31-33]. Different classification systems for junctional tumors may contribute to these different findings, however, whether

adenocarcinomas of the EGJ have heterogeneous etiologies, although of great academic and surgical importance, is not the main concern of this article. In this study, we are interested in the rationality of guidelines for cancer screening programs carried out in these high-risk regions for UGIC. Currently, there are two screening schemes for EGJ cancers: one is combined with esophageal cancer screening *via* endoscopic biopsy examinations with Lugol's iodine staining; the other is combined with gastric cancer screening using the serum pepsinogen test and endoscopy. Regardless of the clustering of UGIC and similar endoscopy methods adopted in screening, no program or study has focused on integrating screening for esophageal, junctional and gastric cancers together in one examination. In our study population, for example, the number of missed diagnoses may have been reduced if a serum pepsinogen test and/or questions regarding family history of UGIC and gastrointestinal symptoms had been used as a primary screening method before endoscopy.

Observations of an asymmetrical circumferential distribution of lesions in the gastrointestinal tract are not uncommon. For instance, the uneven distribution of benign gastric ulcers, primarily found on the lesser curvature or the anterior and posterior walls close to the lesser curvature, has offered crucial information to distinguish benign and malignant gastric ulcerative lesions. When it comes to the circumferential asymmetry in the formation of pathological lesions at the EGJ, the mechanism is largely unknown. One possible explanation is that the pressure on the left posterior side of the lower esophageal sphincter (LES), an important antireflux barrier, is higher compared to the right anterior side, which may also be the reason why reflux esophagitis, Barrett's esophagus and Barrett's esophagus-related cancers are more frequently found on the right anterior wall^[12]. However, the prevalence of esophagogastric reflux disease, Barrett's esophagus and esophageal adenocarcinoma are relatively low in East Asia compared to Western countries^[34,35]. EGJ cancers are significantly associated with *H. pylori*-induced atrophic gastritis in Chinese patients^[20,21]. Whether the asymmetrical circumferential pressure of the LES could also play a significant role in the development of EGJ lesions in Asian high-risk populations requires further investigation. The main concern in this study is whether identification of the asymmetrical circumferential distribution of lesions at the EGJ or the so-called high incidence spot could be used in the design of screening guidelines for this cancer in high-risk populations. Our study assessed the effect of additional routine biopsies from this specific site at the EGJ and found that routine biopsies can improve the detection rate. However, biopsies from 125 (37396/300) subjects are needed before identifying one positive case based on our study, while biopsies from 17 (3405/206) subjects are needed to identify one positive case if biopsies are only taken from areas with mucosal abnormalities at the EGJ. These findings provide crucial information for other countries with a high incidence of EGJ cancers, especially when national health authorities attempt to adopt endoscopy as a

primary detection procedure in mass screening programs, such as in Iran, Japan or South Africa. Instead of trying to identify all potential patients, training enough qualified endoscopists as well as pathologists for understaffed local hospitals may be a more cost-effective and wise option.

Certain weaknesses in our study merit further discussion. First, this was a cross-sectional study conducted in eight high-risk regions, however, the number of villages selected varied among the counties. In Linzhou, one of the most well-established cancer prevention centers, five villages were selected and enrolled the largest proportion of total participants (18.08%) due to their very experienced screening team with sufficient personnel and working capacity. Whereas, in Feicheng two villages were selected and only made up 8.00% of total subjects due to limited study resources. This uneven sampling could have resulted in heterogeneity within our study population. However, the purpose of this study was not to compare frequency distributions by counties, and the descriptive analysis of demographic characteristics showed similar mean ages and sex ratios (Table 1). Second, biopsies obtained from subjects with normal-appearing mucosa were all targeted at the high incidence spot of EGJ cancers, whereas biopsies from participants with mucosal abnormalities were only taken from visible lesions regardless of the anatomic sites at the EGJ. If all subjects had been biopsied from the high incidence spot of junctional cancers, we would have had more information regarding the prevalence of lesions at this site. Nevertheless, the aim of our study was not to investigate the prevalence of lesions originating from the high incidence spot. Furthermore, it would not have been ethical or efficient to obtain unnecessary biopsies from participants given the primary goal of our study was to reduce the overall risk involved with endoscopic screening for EGJ cancers. Third, the diagnostic criterion for EGJ cancers in this study was tumors with an epicenter lying at the EGJ, or within 1 cm proximally and distally. This diagnostic criterion is largely based on the assumption that endoscopists can identify the EGJ at endoscopy, which is defined as the most proximal extent of the gastric folds. However, this landmark is affected by patients' constantly changing physical conditions such as respiration, gut motor activity, and the degree of distention of the esophagus and stomach^[36]. Our diagnostic criteria for EGJ cancers were mainly derived from the previous widely used concept, gastric cardia cancer, and revised according to the Siewert type II junctional cancer. However, it is conceptually unclear why the definition of EGJ cancer should be limited to within 1 cm distal and proximal to the EGJ. Despite its shortcomings and given the absence of compelling evidence for a universally accepted definition or diagnostic criteria, we continued to use the current definitions described above.

In summary, this is the first multicenter, population-based study to investigate the role of routine biopsies from normal-appearing mucosa at the high incidence spot of EGJ cancers when screening for junctional adenocarcinomas. Our findings did not support the use of routine biopsies from this specific site to detect HIN or

higher-grade lesions in high-risk populations without visible mucosal lesions. In contrast, visible mucosal abnormalities of the EGJ are strongly associated with positive pathologic diagnoses and it is advisable to consider these pathological manifestations as an indication for biopsies during endoscopic examinations. As a direct result of our findings, the guidelines for EGJ cancer screening in China have already been adapted to reduce unnecessary risks and expenditure. However, further studies are needed to identify less invasive methods for the primary prevention of junctional cancers in order to reduce the overall rates of missed diagnoses. In addition, follow-up studies are necessary to examine the impact of screening guidelines on cancer mortality, the ideal age of screening initiation, the optimal intervals for repeat examinations, and appropriate follow-up for patients with different precancerous lesions.

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COMMENTS

Background

An asymmetrical circumferential distribution of esophagogastric junction (EGJ) cancers has been described in Chinese, Iranian and Japanese patients. This circumferential asymmetry of pathological lesions at the EGJ led to the identification of a high incidence spot of junctional lesions which is at the right anterior side of the EGJ at endoscopy, specifically at the most proximal gastric rugae of the lesser curvature. However, whether identification of the high incidence spot could be used in mass endoscopic screening in high-risk populations to increase the detection rate of high-grade intraepithelial neoplasia or higher grade lesions is largely unknown.

Research frontiers

Observations of an asymmetrical circumferential distribution of lesions in the gastrointestinal tract are not uncommon. However, the mechanism of the circumferential asymmetry in the formation of pathological lesions at the EGJ is largely unknown. One possible explanation is that the pressure on the left posterior side of the lower esophageal sphincter (LES), an important antireflux barrier, is higher compared to the right anterior side, which may also be the reason why reflux esophagitis, Barrett's esophagus and Barrett's esophagus-related cancers are more frequently found on the right anterior wall. However, the prevalence of esophagogastric reflux disease, Barrett's esophagus and esophageal adenocarcinoma are relatively low in East Asia compared to Western countries. EGJ cancers are significantly associated with *Helicobacter pylori*-induced atrophic gastritis in Chinese patients. Whether the asymmetrical circumferential pressure of the LES could also play a significant role in the development of EGJ lesions in Asian high-risk populations requires further investigation.

Innovations and breakthroughs

The aim of the study was to clarify the existing controversy among doctors regarding the use of routine biopsy of the high incidence spot of the EGJ using

population-level data. This study determined whether identification of the asymmetrical circumferential distribution of lesions at the EGJ or the so-called high incidence spot could be used in the design of screening guidelines for this cancer in high-risk populations. The study assessed the effect of additional routine biopsies from this specific site at the EGJ and found that routine biopsies can improve the detection rate, but unnecessarily exposed the majority of participants to the risks of biopsy, compared with taking biopsies only from those with visibly abnormal mucosa. When adjusted for potential confounders, a strong association between visible mucosal abnormality and a positive pathologic result was also observed in the multivariate analysis. Compared with participants who showed normal-appearing mucosa at endoscopy, the risk for high-grade intraepithelial neoplasia or higher grade lesions was 32 times higher in patients with visible lesions at the EGJ.

Applications

This study suggests that routine biopsies from the high incidence spot of EGJ cancers are of limited value and are unjustified. Visible mucosal abnormalities of the EGJ are strongly associated with positive pathologic diagnoses, and it is advisable to consider these pathological manifestations as an indication for biopsies during endoscopic examinations. The findings provide crucial information for other countries with a high incidence of EGJ cancers, especially when national health authorities attempt to adopt endoscopy as a primary detection procedure in mass screening programs, such as in Iran, Japan or South Africa. Instead of trying to identify all potential patients, training enough qualified endoscopists as well as pathologists for understaffed local hospitals may be a more cost-effective and wise option.

Terminology

Esophagogastric junction cancers: esophagogastric junction cancers are tumors with an epicenter lying at the esophagogastric junction, or within 1 cm proximally and distally.

Peer review

This is a multicenter study that was aimed to explore whether routine biopsies at the high incidence spot of esophagogastric junction cancer were justified in endoscopic screening.

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