

The prevalence of Barrett's esophagus remains low in Eastern China

Single-center 7-year descriptive study

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ABSTRACT

الأهداف: اختبار نسبة انتشار مريء باريت بين سكان الصين الشرقية والذين خضعوا للتنظير المعدي.

الطريقة: أُجريت هذه الدراسة في مستشفى درام التابع للكلية الصحية بجامعة نانجينغ، الصين وذلك خلال الفترة من يناير 2005م إلى يناير 2012م. شملت الدراسة كافة المرضى المصابين بمريء باريت حيث قمنا بحساب نسبة انتشار المرض باختلاف الأعمار، والتقييم السنوي، وباختلاف الأجناس. كما أننا قمنا بدراسة العلاقة بين مرض ارتجاع المريء المعدي ومرض مريء باريت.

النتائج: لقد قمنا بدراسة ما مجموعه 139,416 مريضاً حيث ثبتت إصابة 234 مريض بمرض مريء باريت (0.168%, 95% CI: 0.146-0.189%). لقد كان متوسط عمر المرضى 61.00 ± 13.98 ، ونسبة الذكور إلى الإناث 130:104. لقد قمنا بتشخيص غالبية المرضى (173) اعتماداً على ظهور تشخيص مريء باريت خلال التنظير، فيما شُخصت 61 حالة بالإصابة بكل من التهاب المريء، وقرحة المريء، والسليبية المريئية، وتآكل المخاط المريئي. ولقد زادت نسبة الإصابة بالمرض مع التقدم في العمر ($X^2=9.25, p<0.0001$). لقد ظهرت غالبية مرض مريء باريت في الجزء السفلي من المريء (92.7%)، والجزء القصير من المريء. وظهرت أعراض ارتجاع المريء المعدي لدى 131 مريض (56%)، كما وكان حمض الجزر من أكثر الأعراض ظهوراً. وخلال فترة المتابعة لم يُصب أي من المرضى المصابين بمريء باريت بالسرطان الغدي.

خاتمة: أظهرت هذه الدراسة بأن نسبة انتشار مريء باريت تعد متدنية في العينة التي قمنا بدراستها، كما أن نصف العينة لم تكن مصابة بالارتجاع المعدي المريئي.

Objectives: To detect Barrett's esophagus (BE) prevalence in patients undergoing gastroscopy in Eastern China.

Methods: This study was carried out in Drum Tower Hospital Affiliated Medical College of Nanjing University, Nanjing, China from January 2005 to January 2012. All BE patients were enrolled in the study. The prevalence of BE were calculated generally in different age grades, calendar year, and by gender. The relationship between gastroesophageal reflux disease (GERD) symptoms and BE were also studied.

Results: During the study period, 139,416 patients were studied and 234 patients (0.168%, 95% confidence interval, 0.146%-0.189%) were identified as BE. The mean age was 61.00 ± 13.98 years, and the male to female ratio was 130:104. Most cases (173) were diagnosed due to endoscopic BE features; however, 61 were diagnosed with esophagitis, esophageal ulcer, esophagopolypus, and esophageal mucosa erosion. The prevalence increased with aging ($\chi^2= 9.25, p<0.0001$). Most BE were located in the lower segment of the esophagus (92.7%) and short-segment BE. Gastroesophageal reflux disease symptoms were found in 131 patients (56%) and acid regurgitation was the most common symptom. Over a follow-up period, no BE developed to esophageal adenocarcinoma.

Conclusions: The prevalence of BE in the studied population was very low. Approximately half of them show no signs of GERD symptoms.

Saudi Med J 2012; Vol. 33 (12): 1324-1329

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Received 25th June 2012. Accepted 7th October 2012.

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Barrett's esophagus (BE) is an acquired disorder in which normal squamous epithelium of distal esophagus is replaced by columnar epithelium containing goblet cells.^{1,2} Barrett's esophagus itself seldom causes clinical manifestations, and it has been recognized as the only identifiable precancerous lesion for esophageal adenocarcinoma.^{1,2} The incidence of esophageal adenocarcinoma increased rapidly in western country, which was considered caused by the increasing prevalence of BE during the past 2 decades.³ Thus, more and more attention has been paid on BE. The precise prevalence of BE is still unknown.^{1,2} Previous studies have reported its prevalence from 0.1% to 30%.⁴⁻¹⁵ Usually, BE, also known as esophageal adenocarcinoma, has been observed less frequently in Asia than in Western countries.^{1,2} In Swedish population⁸ the prevalence was approximately 1.6% and 0.7% in American population.⁹ Another study carried out in American asymptomatic individuals (>50 years) showed that BE prevalence was as high as 25%.⁷ In Asian countries, Korea, and Japan reported that the prevalence in general population was approximately 0.22-1.2%.^{6,10} In Chinese population reports coming from Taipei and Hong Kong indicated that the prevalence of BE was approximately 0.1%.^{4,5} The great differences among these researches may be derived from the different ethnicity and races, the nature of the population studied, the indication for endoscopy, the biopsy methods, the sample size, and the definition of BE.^{7,9,14} At present, the prevalence of BE in Chinese mainland population remains obscure. Peng et al¹¹ and Xiong et al,¹² who come from the same medical center in Southern China, reported the prevalence of BE was approximately 1%. However, another China research, which was carried out in Western China, reported the prevalence was high as 30%.¹³ What caused the great difference was still unknown. Thus, the aims of the present study were to determine the prevalence of BE in China-east population who underwent gastroscopy.

Methods. This study was carried out in Drum Tower Hospital Affiliated Medical College of Nanjing University, Nanjing, China from January 2005 to January 2012. Patients' inclusion criteria for this

Disclosure. This study was funded by the Jiangsu Province Social Development Foundation (BS2006011) and Nanjing Medical Science and Technique Development Foundation (201142), Nanjing, China. Authors have no conflict of interests, and the work was not supported or funded by any drug company.

study were consecutive patients older than 18 years underwent gastroscopy for any indications at our endoscopic center. The exclusion criteria were patients who had incomplete and duplicate reports, patients who underwent therapeutic or urgent upper endoscopies, and patients who had previously undergone gastrectomy or esophagectomy. If patients underwent the examination for more than once during the study period, only the first or the time he/she had been identified as BE was included. Patients' demographic information, such as age, gender, ethnicity, height, and weight, were collected. All patients were followed up by telephone regularly after the diagnosis.

The protocol of this study was prepared according to the recommendations of the declaration of Helsinki and the study was approved by the Ethics Committee of Medical School of Nanjing University, Nanjing, China. All participants were given written informed consents.

Endoscopy. All endoscopic procedures were performed by experienced and professional endoscopists using an Olympus GIF XQ240 or GIF H260 gastroscope (Olympus, Tokyo, Japan). The gastroesophageal junction (GEJ) was defined as the junction of the proximal gastric folds and the tubular esophagus. Patients were determined to have endoscopically suspected BE (ESBE) if salmon-colored columnar-appearing mucosa presented over the GEJ regardless where the abnormal mucosa was located. Long segment BE (LSBE) and short-segment BE (SSBE) were defined as the columnar epithelium ≥ 3 cm and < 3 cm above GEJ.¹⁰ A diagnosis of hiatal hernia was made when the distance between the diaphragmatic crux and esophago-gastric junction exceeded 2 cm. Esophagitis was defined and graded according to the Los Angeles classification system.¹⁶ The length from incisor teeth to the lesion during endoscopy were 24 cm (upper segment of esophagus), 24-32 cm (middle segment) and more than 32 cm (lower segment). Esophageal ulcer, esophagitis, esophagopolypus, esophageal carcinoma, and other lesion of esophagus were all recorded. Endoscopic data were recorded on the same form for all the individuals. Another 2 experienced researchers reviewed all the endoscopic images and confirmed the diagnosis.

Biopsy and histology. All biopsies were taken by standard commercial available forceps. At least 2 biopsy specimens were taken from the tongue and island-like columnar-appearing mucosa in each endoscopically suspected BE patient. For the circumferential segment, biopsy samples were taken from 4 quadrants at 2 cm intervals if the lesion was more than 2 cm in length. The patients were excluded from this cohort either of esophageal varices, taking anti-coagulation drugs,

important findings (such as active bleeding, cancer in gastric fundus or esophagus) or their denial. Specimens obtained from esophageal mucosa were placed in 10% buffered formalin solution, embedded in paraffin, and stained with hematoxylin and eosin (HE). Biopsy specimens were independently examined by one experienced gastrointestinal pathologist who was blinded to the clinical data and endoscopic findings. The diagnosis of BE was made only if the presence of goblet cells could be identified. Complete intestinal metaplasia of the cardiac mucosa or gastric mucosa was not included in the definition. In all cases, the diagnosis of BE were confirmed by Alcian blue stain (pH 2.5). Once dysplasia was identified in BE patients, low-grade dysplasia (LGD) and high-grade dysplasia (HGD) should be identified. For patients with HGD, endoscopic resection was advised. If therapeutic was undertaken, the patients were monitored, and followed regularly.

Protocols and related definitions. Patients were enrolled in this cohort once endoscopic features of BE were found. Symptoms suggestive of gastroesophageal reflux disease (GERD), including heartburn, chest pain, and acid regurgitation (at least one episode per week in recent 3 months) were also identified and recorded. The diagnosis of GERD was made if GERD questionnaire (GERDQ) score more than 8. Some patients, even without endoscopic features of BE, but for other reasons biopsies were taken from esophagus and histologically confirmed as BE, were also enrolled in this research program. The *Helicobacter pylori* (*H. pylori*) infection status was determined using rapid urease test (RUT) on antral biopsy specimens, the samples change to red was considered positive.¹⁷ Simultaneously, Giemsa staining was employed to confirm the results of RUT. In any condition if Giemsa staining was positive, the patient was diagnosed as *H. pylori* infection.

Statistical analysis. Ninety-five percent confidence intervals (95% CI) for the estimated prevalence were calculated using the Poisson distribution. The prevalence in different age-grades were compared using Cochran Armitage trend test. Differences among yearly detailed prevalence and gender prevalence were compared using χ^2 statistics. *P* values were all 2 tailed and the level of significance was set at 0.05. Statistical Analysis Software Version 9.2 (SAS Institute, Cary, NC) software was used for all the analyses.

Results. During the study period, 139,416 certified individuals received a screening gastroscopy in our endoscopic center. Among them, salmon-colored

columnar-appearing mucosa over the GEJ was found in 2184 cases (1.6%) and in these patients (except for 158 cases in which biopsies were not performed) 173 cases of BE were confirmed histologically. Another 61 BE cases were diagnosed because of other endoscopic indications of esophagitis (n=47), esophageal ulcer (n=7), esophagopolypus (n=6) and esophageal mucosa erosion (n=1). A total of 234 cases were eventually confirmed of BE. The mean age of BE patients was 61.00±13.98 years and there were no difference between the 2 genders (male: 58.50±14.14, female: 62.00±13.84, *p*=0.770). Among the 234 BE cases, 122 cases (52.1%) were *H. pylori* positive, 131 (56%) cases complained the symptoms of GERD and 19 (8.1%) cases were diagnosed of hiatal hernia.

The prevalence of BE in this population was 0.168% (95% CI: 0.146-0.189%). During the study period, the cases that undergoing gastroscopy increased annually, the ratio of endoscopic suspected BE and histologically confirmed BE were stable (Table 1).

Among BE patients, there were 104 female and 130 male. The prevalence in female was 0.156% (95% CI: 0.135-0.176%) and male was 0.176% (95% CI: 0.154-0.198%). No statistical difference was found ($\chi^2=0.897$, *p*=0.344). The ratio of endoscopic suspected BE (ESBE) did not increased with aging, the prevalence of histologically confirmed BE increased gradually with aging, and significant differences were found in different age grades ($\chi^2=9.25$, *p*<0.0001). The age and gender distributions and its corresponding prevalence were shown in Table 2.

In BE cases, the lesions were located in the upper (1.3%), middle (6%) and lower (92.7) segment of esophagus. Of the 173 cases, that shows salmon-

Table 1 - Prevalence of Barrett's esophagus (BE) in different calendar years.

| Year | N | Endoscopic suspected BE | | Histologically confirmed BE | |
|-------|--------|-------------------------|---------------|-----------------------------|---------------|
| | | Prevalence % | 95% CI | Prevalence % | 95% CI |
| 2005 | 13977 | 1.502 | 1.439 - 1.566 | 0.215 | 0.190 - 0.239 |
| 2006 | 16234 | 1.521 | 1.457 - 1.586 | 0.123 | 0.105 - 0.142 |
| 2007 | 18437 | 1.752 | 1.683 - 1.821 | 0.141 | 0.121 - 0.161 |
| 2008 | 20896 | 1.890 | 1.819 - 1.962 | 0.139 | 0.119 - 0.158 |
| 2009 | 21617 | 1.198 | 1.141 - 1.255 | 0.171 | 0.149 - 0.193 |
| 2010 | 22615 | 1.251 | 1.193 - 1.310 | 0.226 | 0.201 - 0.250 |
| 2011 | 25640 | 1.366 | 1.305 - 1.427 | 0.160 | 0.139 - 0.181 |
| Total | 139416 | 1.453 | 1.390 - 1.516 | 0.168 | 0.146 - 0.189 |

During the past 7 years, cases undergoing gastroscopy increased annually, the ratio of endoscopic suspected BE and histologically confirmed BE were not changed, 95% CI - 95% confidence intervals.

Table 2 - Prevalence of Barrett's esophagus (BE) in different age grades and genders.

| Variables | N | Prevalence of ESBE | | P-value | Prevalence of HCBE | | P-value |
|---------------|---------|--------------------|---------------|---------|--------------------|---------------|---------|
| | | % | 95% CI | | % | 95% CI | |
| <i>Gender</i> | | | | 0.889 | | | 0.405 |
| Male | 73,327 | 1.428 | 1.366 - 1.490 | | 0.176 | 0.154 - 0.198 | |
| Female | 66,089 | 1.481 | 1.418 - 1.545 | | 0.156 | 0.135 - 0.176 | |
| <i>Age</i> | | | | <0.001 | | | <0.0001 |
| 18-29 | 12,804 | 0.773 | 0.727 - 0.819 | | 0.023 | 0.015 - 0.031 | |
| 30-39 | 21,890 | 1.138 | 1.082 - 1.193 | | 0.078 | 0.063 - 0.092 | |
| 40-49 | 30,270 | 1.652 | 1.585 - 1.719 | | 0.116 | 0.098 - 0.135 | |
| 50-59 | 33,183 | 1.820 | 1.750 - 1.890 | | 0.163 | 0.142 - 0.184 | |
| 60-69 | 23,474 | 1.359 | 1.298 - 1.420 | | 0.264 | 0.237 - 0.291 | |
| 70-79 | 14,927 | 1.467 | 1.404 - 1.530 | | 0.281 | 0.254 - .309 | |
| ≥80 | 2,868 | 1.255 | 1.197 - 1.314 | | 0.732 | 0.687 - 0.777 | |
| Overall | 139,416 | 1.453 | 1.390 - 1.516 | | 0.168 | 0.146 - 0.189 | |

For the endoscopic suspected BE (ESBE) cases, no difference was found in different genders.

There was a statistically significant difference between the age grades ($p < 0.001$). In the histologically confirmed BE (HCBE) group, no difference was found in the 2 genders; however, a significant difference was identified in different age grades (Cochran Armitage trend test).

Table 3 - Gastroesophageal reflux disease (GERD) related symptoms and duration in different groups.

| Symptoms | ESBE group n (%) | No-ESBE group n (%) | P-value |
|-----------------------|---------------------|---------------------------|---------|
| Indicated no symptoms | 94 (54.4) | 9 (14.8) | <0.0001 |
| Indicated symptoms | 79 (45.7) | 52 (85.3) | |
| Heart burn | 18 | 14 | |
| Chest pain | 17 | 7 | |
| Acid regurgitation | 44 | 31 | |

In all the 234 Barrett esophagus cases, there were 131 cases show GERD related symptoms. The symptoms in the no endoscopic suspected Barrett esophagus (ESBE) group (n=61) were more common compared with the endoscopic suspected BE group (n=173). Acid regurgitation was the most common symptom.

colored columnar-appearing mucosa over the GEJ and histologically confirmed BE, the lesion mucosa was located in the upper (n=1), middle (n=6), and lower segments (n=166). In the 173 cases, LSBE was identified in 17 and SSBE in 156 cases. All the 17 LSBE individuals were also suffered from hiatal hernia. Six of the 173 cases also suffered esophagitis aside from BE (these case were not included in the 47 cases of simple esophagitis). Of these 53 esophagitis cases, there were 15 cases graded as A, 16 as B, 19 as C, and 3 as D.

There were 131/234 BE cases (56%) GERD related symptoms, but only 17 cases reached diagnostic criteria of GERD (GERDQ score more than 8). Gastroesophageal reflux disease related symptoms were more common in no- endoscopic suspected BE group than in endoscopically suspected and histologically confirmed BE group (Table 3). The most common symptom was acid regurgitation. In most patients

GERD related symptoms lasted for more than 6 months (53.4%).

There were cases in the 234 BE patients indicated low-grade dysplasia (n=11) and high-grade dysplasia (n=7). The mean follow-up period for the low-grade dysplasia patients was 33 months (from 7-78 months). One patient developed a high-grade dysplasia when followed to 70 months and endoscopic mucosa resection was undertaken. Six of the 7 HGD patients underwent endoscopic therapy (3 underwent argon plasma coagulation therapy and 3 underwent endoscopic mucosa resection), another case was followed for 11 months, and no malignant was identified. The mean follow-up time for all BE patients was 31 months (from 3-84 months). During follow-up period no esophageal adenocarcinoma (EAC) was confirmed.

Discussion. The study presented herein identified that the prevalence of histologically confirmed BE was 0.168% (95% CI: 0.146-0.189%). Even though there was no significant gender difference in this population, it increased with aging. Most lesions located in the lower segment of the esophagus and LSBE was less common than in western countries. Neither all the BE patients show typical endoscopic salmon-colored columnar-appearing mucosa nor all patients experienced GERD related symptoms. The most common symptom was acid regurgitation. During follow-up, no malignant change was identified.

Barrett's esophagus prevalence ranged widely from 0.06-25%.⁴⁻¹⁵ Its prevalence in western countries was higher than in eastern countries has been considered to be caused by different ethnicity and race.^{1,2,18} However,

prevalence also ranged widely in Asian countries.^{4-6,14,15} What causes the differences in Asian countries is still unknown, despite of the disease etiologies, the following factors during the study should be considered such as the studied population, the diagnostic criteria of BE, the methods of biopsy, the sample size, the study design and gastroscopy rates and so forth.

It is obviously that the different studied population indicated different BE prevalence. Some of the previous researches were carried out in selected population and some in general population.^{4-15,19-21} In the past decades, the diagnostic criteria of BE had changed a lot, even now whether intestinal metaplasia (IM) should be included in the diagnosis of BE is in debate.²² In some studies, special intestinal metaplasia or gastric metaplasia were considered as BE,^{4,8,10} however, in some other studies only intestinal metaplasia with goblet cells was considered as BE.^{9,19} The different histological diagnostic criteria of BE may be the most important factor influencing BE prevalence during the study process. It has been suggested that biopsy should be taken from 4 quadrants with 1-2 cm interval.²² However, in most studies, biopsy was not carried out.^{4,10,19,20} Besides, increased BE prevalence maybe caused by increasing gastroscopy rates.^{22,23} Prospectively, random large sample size study carried out in multi-center with standard biopsy method can draw more credible results, but very few studies have been consistent with all these aspects. Different studies carried out in China also have different prevalence.^{4,5,11-13} Methods of biopsy in these studies were similar with Chinese studies. Studied population, diagnostic criteria, and sample size maybe the reason caused the difference. In some studies, the sample size were quite small,¹¹⁻¹³ and they only included symptomatic individuals. In previous study,¹⁴ the sample size was large that the diagnostic criteria was different from ours, due to the reason that they included the gastric and cardiac mucosa metaplasia. We are not sure whether the higher prevalence in western countries was caused by the higher gastroscopy rates, but in our study, the gastroscopy rates gradually increased in the past 7 years (Table 1). Gastroscopy rates increased gradually, but histologically confirmed BE did not increased at the same time period. The mean age was similar to other studies,^{4-15,19,20} when comparing to patients of the same age grades, and its prevalence in this studied population was also fairly low. The studies carried out in the USA among older people (≥ 65 years) indicated that its prevalence was 16.7%,²¹ and among asymptomatic older individuals (>50 years) was as high as 25%.⁷ However, the corresponding prevalence in current study were 0.321% and 0.240% respectively (data not

shown). In most studies, it has been reported that BE was prominent in male patients.^{1,2,21,24} However, in our study the male/female ratio was almost equal (male to female ratio = 130:104, $\chi^2=0.897$, $p=0.344$).

The coincidence rate of endoscopically suspected and histologically confirmed BE in our study was lower than in previous study (8.54% versus 20.74%).^{22,23,25,26} Bastard biopsy method was used and considered as the culprit. However, if taken the age grade into account, the coincidence rate in this study was as high as 21.8% in patients elder than 60, 24.7% in 70 years, and 58.3% in 80 years old. From this point of view, biopsy method may be not the culprit, which caused the low coincidence rate. Further analysis, we found that the endoscopic suspected BE ratio did not increased with aging; however, the histologically confirmed BE ratio increase with aging. This may indicate that the salmon-colored columnar-appearing mucosa over the GEJ could exist for many years before it changed to complete intestinal metaplasia. The persistent acid exposing may be the fundament causing of this change. This could explain why the coincidence rate increased with aging.

Similar to previous report, many BE patients in our studied population did not show GERD related symptoms, and some esophagitis patients were found to have BE on second endoscopy.^{4,5,7,27} In our study, some BE patients indicated endoscopically as esophagitis, esophageal ulcer, and esophagopolypus. These data suggested that BE may have different endoscopic features, and repeated endoscopy may improve the diagnosis of BE. *Helicobacter pylori* positive was confirmed in approximately half of the BE patients in current study. No difference was identified between the BE patients and the whole study population. Prague C & M criteria was a new classification and was considered as more reliable for LSBE, but less reliable for SSBE.^{28,29} In current study, we did not employ this criteria as most cases of BE in current study were SSBE.

Study limitations. Our results are credible for a large sample of patients. Firstly, our study was single center; this may cause population selection bias. Secondly, just like Ronkainen et al,⁹ to study the prevalence in general population, all individuals should be identified randomly, but in our study individuals were not identified randomly. The future research should performed based on a random process such as community individuals.

In conclusion, BE was identified in 0.2% of the adult population who undergoing gastroscopy in China-east. Most BE patients were SSBE and show no GERD related symptoms.

Acknowledgment. We would like to give a special thanks to Dr. Biyun Xu for her prominent work in the statistical analysis. Also, we would like to thank foreign students Mr. Sachin Mulmi and Ms. Sagun Bajracharya for their help in preparing the manuscript.

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