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Current Status of Barrett's Esophagus Research in Asia

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Abstract

In Western countries, the epidemiology of esophageal cancer has changed markedly over the past several decades with squamous cell carcinoma undergoing a rapid decline and adenocarcinoma progressively increasing. Although the prevalence of gastroesophageal reflux is increasing in Asia, the prevalence of Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC) have so far remained low in most Asian countries for which data are available. This provides a unique opportunity for research into the initiating factors of BE and EAC. The Asian Barrett's Consortium recently conducted a review of published studies on BE from Asia to assess the current status of BE research in Asia, and to recommend potential areas for future BE research in the region. Differences in study design, enrolled population, and endoscopic biopsy protocols used have led to substantial variability in the reported BE prevalence (0.06% to 19.9%) across Asia. As has been observed in Western countries, increased age, male sex, tobacco smoking, reflux symptoms, and erosive esophagitis have been found to be risk factors for BE in several case-control studies from Asia. The Prague C and M criteria, developed to provide better interobserver reliability in diagnosis and grading of BE, are currently under extensive evaluation of their applicability in the Asian population. The Asian Barrett's Consortium believes that only after adequate reliability in endoscopic and histological diagnosis has been demonstrated will Asian clinicians initiate collaborative projects to identify etiologic determinants of BE and its ensuing malignant transformation. At present, data regarding the management and long-term outcome of BE are extremely limited in Asia. More studies of BE in this geographic area are warranted.

Keywords

Barrett's esophagus; prevalence; risk factor; gastroesophageal reflux disease; esophageal adenocarcinoma

Introduction

Barrett's esophagus (BE) was first described more than 50 years ago.¹ The condition is generally hypothesized to be a consequence of gastroesophageal reflux disease (GERD),² and to have the potential to develop into esophageal adenocarcinoma (EAC).^{3–5} In Western countries, the epidemiology of esophageal cancer has changed over the past few decades whereby the occurrence of squamous cell carcinoma has decreased while that of EAC has increased.^{6–8} The upward trend of EAC is thought to be due to increasing prevalences of GERD, BE, obesity, and changes in diet and life-style.^{3, 9–11} Because of poor 5-year survival rates for EAC, surveillance for BE has become a critical issue.^{12–14}

In Asia, although an increasing incidence of GERD has been noted in recent years, BE and EAC appear rare.^{15–22} Based on inference from epidemiologic data generated from Western countries, it is foreseeable that incidence of BE in Asia could rise. In view of this, the U.S. National Cancer Institute organized an Asian Barrett's esophagus workshop in 2008, and this was attended by an international group of experts in the field of upper gastrointestinal malignancies. The workshop provided the impetus to form an Asian Barrett's Consortium among its attendees. The main purpose of the consortium was to provide a forum for sharing ideas and resources that would enable these experts to develop collaborative strategies to identify etiologic determinants of BE and its ensuing malignant transformation in Asia. The consortium recently conducted a review of published studies on BE from countries in Asia to assess what is known about the prevalence, risk factors, diagnosis, long term follow-up, and management of BE in Asia, to identify the shortcomings and gaps in BE research, and thereafter to recommend potential areas for future research in BE in the region. This manuscript reports our findings.

Epidemiology

Prevalence

According to the American College of Gastroenterology guidelines,²³ BE is defined as a change in the distal esophageal epithelium of any length that can be recognized as columnar type mucosa at endoscopy and is confirmed to have intestinal metaplasia by biopsy of the tubular esophagus. Based on this definition, the prevalence of BE in Asia outside Japan ranges from 0.06% to 6.2% (Table 1).^{24–33} In Japan, the prevalence of BE is reportedly as high as 19.9% in a series where biopsy was employed³⁴ and as high as 43% in those series without biopsy.^{21, 35–37} The different definitions of the esophagogastric junction (EGJ) might, to a large extent, account for this discrepancy. Most studies from Asia outside Japan used the proximal margin of the gastric folds as the EGJ; however, the distal margin of palisade vessel was usually used as the landmark for the EGJ in the Japanese studies.^{33, 38} Furthermore, in contrast to studies from Western countries, most Asian studies did not use a standardized four-quadrant biopsy protocol. Hence, it is possible that the prevalence of BE has been underestimated in Asia outside Japan, and this should be considered when interpreting the data on the prevalence of BE. Recently, two studies using the standardized four-quadrant biopsy protocol were reported from Korea and Taiwan.^{32, 33} While the Korean study population comprised entirely subjects presenting for routine health check-up, the Taiwan study population comprised both subjects undergoing routine health screening and patients presenting with upper abdominal symptoms. The prevalence of endoscopically-

suspected esophageal metaplasia (ESEM) and histologically-proven BE were 3.4% and 0.84% in the Korean study,³³ and 1.9% and 0.85% in the Taiwan study,³² respectively. In Taiwan, two studies on the prevalence of BE performed by the same group have been published. One study³¹ was performed retrospectively involving at least two biopsies while the other study³² was performed prospectively using the standardized four-quadrant biopsy protocol. The prevalence of ESEM and histologically-proven BE were 0.28% and 0.06% in the retrospective study, and 1.9% and 0.85% in the prospective study, respectively. A recent study found a 0.5 % prevalence of Barrett's esophagus amongst adult Chinese undergoing health screening.³⁹ Together, these results indicate the importance of study design and biopsy protocol when determining the prevalence of BE.

In Japan, the distal limit of the lower esophageal palisade vessels is usually regarded as the EGJ and the designated area of the columnar-lined esophagus (CLE) is anatomically defined by the distal limit of the lower esophageal palisade vessels (LEPV). Further, the term 'Barrett's esophagus' is used interchangeably with "CLE". This may explain the high prevalence of BE in some reported series from Japan.^{35–37} In a study on patients undergoing surgical resection for squamous cell carcinoma of the esophagus, Ogiya *et al*⁴⁰ found that preoperative endoscopy revealed CLE in half of all patients and that in the resected specimens, the distal limit of the LEPV was lower than the squamo-columnar junction in 95.2% of patients. Almost all cases had CLE based on the Japanese criteria. Most of the CLE areas were very short; their average maximum length was only about 5 mm. In addition, no intestinal metaplasia was observed in any of the CLE cases.

The increase in EAC in Western countries is widely recognized. In contrast, the incidence of EAC is declining in Hong Kong⁴¹, remains unchanged in Taiwan,⁴² and increasing slowly in Singapore.⁴³ In Asian patients, esophagitis does exist, but BE is infrequently diagnosed and most of such diagnoses are short-segment Barrett's esophagus (SSBE).^{32,36,37}

In summary, published studies on the prevalence of BE from Asia showed wide ranging data and these reflect several limitations in the current studies. Firstly, most are retrospective studies^{25, 30, 31} in which there is the possibility that ESEM might not be noted during endoscopy, and this might have led to underestimation of BE prevalence. Secondly, the study population might not be representative of the general population as most studies were performed in single tertiary care referral centers. Thirdly, the endoscopic diagnostic criteria for BE varied among studies. As highlighted previously, determining the EGJ is very important for diagnosing BE and unified criteria are necessary. Some Asian studies, however, used the proximal margin of gastric folds while other studies used the distal margin of palisade vessel as the EGJ. This difference alone could result in miscalculation of the prevalence of BE. Fourthly, most Asian studies did not use a standardized four-quadrant biopsy protocol, which is likely to result in underestimation of the prevalence of BE.

To overcome these limitations and to more accurately estimate and compare the prevalence of BE in Asia, consensus on biopsy protocol, endoscopic diagnostic criteria, and pathologic diagnostic criteria should first be established; Such would provide a strong foundation for collaborate, multicenter, prospective, population-based studies of BE across Asia.

Risk factors

Age has been reported as a significant risk factor for BE in various studies in Asia,^{19, 30, 32, 33, 36, 37} and in one study, it correlated with the length of BE.³⁶ The mean age of patients with BE in Asia ranges from 51.1 to 66.7 years.^{22, 29, 32, 36} In addition, reflux symptoms^{30, 36} and erosive esophagitis^{36, 37, 44} had been shown to be associated with BE in Asia. Using a multivariate model that incorporated factors including age, smoking, and erosive reflux disease, Akiyama *et al*³⁷ showed that aging and severe erosive esophagitis were associated

with the progression of BE. Two studies^{30, 37} implicated smoking as a risk factor for BE. Akiyama *et al*⁴⁵ found that alcohol was associated with both erosive esophagitis and BE. These findings are in contrast to those in Western studies,^{46, 47} which reported no significant correlation between smoking or alcohol use and BE. In addition, Okita *et al*³⁶ showed that hiatal hernia was associated with BE and length of BE. Abe *et al*⁴⁸ and Chang *et al*³² reported that *H. pylori* appeared to have an inverse association with BE; however, the sample size of these studies was small. In terms of gender, studies from Asian countries showed that men are more likely to have BE with a male/female ratio of approximately 1.93–2.09.^{22, 32} Body mass index has been associated with BE in Western patients in case control studies.⁴⁹ A retrospective study in Japanese patients with fatty liver disease suggested that obesity was also a risk factor for BE, and the risk seemed to be mediated by abdominal visceral adiposity.⁵⁰

Diagnosis

Endoscopic diagnosis

There are few studies addressing the endoscopic diagnosis of BE in Asia (Table 2). Endoscopic reliability was tested in only two trials by Amano *et al*³⁸ and Wong *et al*⁵¹. Neither of these studies, however, evaluated the reliability of the Prague C and M criteria.

Amano *et al*³⁸ compared the degree of diagnostic variability amongst Japanese endoscopists diagnosing BE using either the palisade vessels or the top of the gastric folds as a landmark for the distal esophagus. Eighty-four endoscopists assessed 30 static images of patients with BE. Endoscopists were requested to identify the distal end of the esophagus first using the Japanese criteria (i.e., the palisade vessels) and later using the top of the gastric folds both before and after an explanation of the Prague C and M criteria. They found that the kappa value for the identification of the distal end of esophagus prior to an explanation of the Prague C and M criteria was only 0.14, and was not related to the experience, board licensure, or special training of the endoscopists. After the explanation of the Prague C and M criteria, the overall kappa value increased to 0.35.

In Singapore, Wong *et al*⁵¹ assessed the interobserver agreement for the diagnosis of erosive esophagitis and endoscopically-suspected BE. Thirty-five video clips were viewed and scored by three endoscopists using the Los Angeles (LA) classification. This group found excellent agreement regarding the presence of esophagitis (mean kappa value: 0.79; range: 0.77–0.82). In this study, 15 patients (42%) had endoscopically-suspected BE and the mean kappa value for diagnosing this lesion amongst the endoscopists was 0.48 (range: 0.39–0.60). A trend for increased agreement was observed as viewings progressed after 16 cases, supporting the importance of training in ensuring consistency in endoscopic diagnosis.

Apart from the two studies, evidence regarding the reliability of endoscopic diagnosis of BE is extremely limited in Asia. The Prague C and M criteria were applied for the screening of BE in the studies conducted by Akiyama *et al*³⁷ and Okita *et al*³⁶ in Japan and Chang *et al* in Taiwan.³² However, these epidemiological studies mainly addressed the prevalence and risk factors of BE. To address the research gap in this area, the Asia Barrett's Consortium recently conducted a multinational trial using video clips of patients with BE to determine the interobserver reliability in grading BE by Asian endoscopists.⁵² The study was done following rigorous training of the endoscopists in the use of the Prague C & M classification for diagnosis and grading of BE. The reliability coefficients for recognition of BE extending ≥ 1 cm were 0.90 (0.80–1.00) and 0.92 (0.87–0.98) for the Prague C and M values, respectively, whereas these coefficients decreased markedly for BE segments < 1 cm, to 0.18 (0.03–0.32) and 0.21 (0.00–0.51), respectively.

Histologic diagnosis

In the American College of Gastroenterology guidelines,²³ BE is defined as the presence of specialized intestinal metaplasia (SIM) within the columnar esophagus. In contrast, the Montreal definition regarded BE as either SIM or gastric metaplasia (GM).⁵³ Most BE studies performed in Asia^{28–30, 34, 47} use SIM as an index of histological diagnosis. Recent studies by Tseng *et al*³¹ and Chang *et al*³² applied the Montreal definition for histological criteria, including the use of both SIM and GM. For the histopathological diagnosis of Barrett's adenocarcinoma, it is necessary to confirm that cancer lesions are surrounded by Barrett's epithelia. It is sometimes difficult, however, to find conclusive evidence of Barrett's epithelium, particularly when biopsy or mucosectomy specimens were examined. The histological characteristics of BE in Asian studies are summarized in Table 3.

Magnifying endoscopy and narrow band imaging have been employed in the diagnosis of BE^{54, 55} while confocal endomicroscopy is able to detect the presence of BE and evaluate the degree of dysplasia.⁵⁶ These imaging modalities help reduce the number of biopsies by increasing the sensitivity of a targeted approach.⁵⁵ In Asia, most cases of BE are SSBE and a large proportion of these are shorter than 1 cm in length.³² The shorter the columnar-lined epithelium is, the lower is the prediction rate of histological SIM. Imaging enhanced endoscopy might be one potential solution to minimize the issues inherent in achieving an endoscopic diagnosis of SSBE. Endo *et al*⁵⁷ suggested that various fine mucosal patterns evident on enhanced magnifying endoscopy that correlate with histological findings and that tubular and villous pit patterns were characteristic of SIM. In a separate study, Takubo *et al*⁵⁸ stained the ESEM area with Lugol's iodine solution and found that squamous islands existed in the columnar mucosa in 18 (78%) of 23 patients. The authors suggested that staining with Lugol's iodine solution, with subsequent biopsy of stained squamous islands, may assist in the diagnosis of short-segment columnar-lined esophagus.

In summary, all subjects with endoscopically-suspected BE should be confirmed by histological diagnosis to avoid overestimation of the prevalence of BE in Asia. That said, two studies^{59,60} suggested that CLE without intestinal metaplasia might be equivalent in malignant potential as BE with intestinal metaplasia and the malignant potential of cardiac and fundic epithelia is not known.

Management and long-term follow-up

In Japan, Okita *et al*³⁶ reported significant extension of Barrett's length over a period of 2 years in 28.0% of 236 patients with histologically confirmed SSBE. Hiatal hernia and reflux symptoms were found to be positive predictors of SSBE extension. Using the Prague C and M criteria, Akiyama *et al*³⁷ analyzed a retrospective cohort study with a mean follow-up period of 60 months (range 24–108 months) and found that 47 (12.6%) of the 374 BE cases exhibited progression. Aging and erosive esophagitis, especially severe erosive esophagitis, were significant contributing factors to the progression of length of Barrett's epithelium. However this could represent the inter-observer variability in measuring the BE length since criteria were not standardized.

In China, Chen *et al*²² performed a systemic review and meta-analysis that included 38 studies encompassing 4,120 subjects with endoscopically-suspected BE. The mean length of follow-up for 492 patients was two years and the incidence of esophageal adenocarcinoma was 0.61 per 100 patient-years of follow-up. Unfortunately, no standardized surveillance protocol could be discerned from this review and the criteria for diagnosis of BE were variable among enrolled studies.

Conclusion

Published data on the prevalence, risk factors, diagnosis, and long term outcome of BE in Asia remain limited at present. We recommend establishing appropriately designed examination protocol, and consensus on endoscopic and pathologic diagnostic criteria before conducting future epidemiological studies on BE.

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Table 1

Summary of the prevalence of Barrett's esophagus in Asia

Author	Country	Year	N	Study population	Diagnosis	Prevalence (%)
Yeh <i>et al.</i> ²⁴	Taiwan	1997	464	Symptomatic [‡]	Endoscopy	2.0
Azuma ²¹	Japan	2000	650	Health screening	Histology	15.7
Wong <i>et al.</i> ²⁵	China	2002	16,606	Symptomatic	Endoscopy	0.06
Nasser-Moghaddam ⁶⁴	Iran	2003	269	Symptomatic	Histology	4.8
Lee <i>et al.</i> ²⁶	Korea	2003	1,553	Symptomatic	Histology	0.3
Rosaída <i>et al.</i> ²⁷	Malaysia	2004	1,000	Symptomatic	Endoscopy	2.0
Rajendra <i>et al.</i> ²⁸	Malaysia	2004	1,985	Symptomatic	Histology	6.2
Kim <i>et al.</i> ²⁹	Korea	2005	992	Symptomatic/Health screening	Histology	3.6
Yilmaz <i>et al.</i> ⁶⁵	Turkey	2006	18,766	Symptomatic	Histology	0.4
Amano <i>et al.</i> ³³	Japan	2006	1,668	Symptomatic/Health screening	Histology	19.9
Sollano ¹⁷	Philippines	2007	15,981	Symptomatic	Endoscopy	4.4
Kim <i>et al.</i> ³⁰	Korea	2007	70,103	Symptomatic/Health screening [‡]	Endoscopy	0.2
Bayraktar <i>et al.</i> ⁶⁶	Turkey	2008	160	Symptomatic (reflux symptoms)	Histology	2.0
Tseng <i>et al.</i> ³¹	Taiwan	2008	19,812	Health screening	Histology	0.061
Okita ³⁶	Japan	2008	5,338	Symptomatic/Health screening	Endoscopy	37.4
Akiyama ³⁷	Japan	2009	869	Health screening	Endoscopy	43.0
Chang <i>et al.</i> ³²	Taiwan	2009	4,797	Symptomatic/Health screening	Histology	0.85
Park <i>et al.</i> ³⁴	Korea	2009	25,536	Symptomatic/Health screening	Histology	0.84

[‡] Symptomatic: Esophagogastroduodenoscopy (EGD) for various gastrointestinal complaints including symptoms associated with reflux

[‡] Health screening: EGD for health check up

Table 2

Summary of the classification, validation, and limitation of endoscopic diagnosis for Barrett's esophagus in Asia

Author	SSBE/LSBE	Prague C and M criteria	Reliability
Amano <i>et al.</i> ³³	98.5	Yes [*]	Yes (landmark for EGJ)
Akiyama <i>et al.</i> ³⁷	92.5	Yes [*]	No
Okita <i>et al.</i> ³⁶	199.7	Yes [*]	No
Wong <i>et al.</i> ⁵³	No	No	Yes (GERD grading and/or BE)
Chang <i>et al.</i> ³²	3.1	Yes [†]	No

^{*} Lack of detailed methods or results

[†] The proportion of BE from subjects with ESEM were 38.9% with C≤1M1, 40% with C≤1M2, and 76.9% with CxM≥3 using the Prague C and M criteria.

Abbreviations: EGJ = esophago-gastric junction; GERD = gastroesophageal reflux disease; BE = Barrett's esophagus, SSBE = short-segment BE; LSBE = long-segment BE.

Table 3

Summary of the histological diagnostic criteria for Barrett's esophagus and presence of dysplasia or adenocarcinoma

Author	<u>Histological Criteria for BE</u>		Dysplasia [†]	Adenocarcinoma [†]
	SIM	SIM+GM		
Lee <i>et al.</i> ²⁶	Yes		0/5	0/5
Rajendra <i>et al.</i> ²⁸	Yes		4/123	0/123
Kim <i>et al.</i> ²⁹	Yes		N/A	N/A
Amano <i>et al.</i> ³³	Yes		13/333	5/333
Tseng <i>et al.</i> ³¹		Yes	0/12	0/12
Park <i>et al.</i> ³⁴	Yes		N/A	N/A
Chang <i>et al.</i> ³²		Yes	9/41	1/41

[†]The denominator stands for the total numbers of BE cases and the numerators stand for the BE cases with dysplasia and adenocarcinoma, respectively.

Abbreviations: BE = Barrett's esophagus; SIM = specialized intestinal metaplasia; GM = gastric metaplasia.