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CLINICAL REVIEW

Carcinogenesis of Barrett's esophagus: a review of the clinical literature

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Abstract Barrett's esophagus (BE) is a premalignant condition of esophageal adenocarcinoma (EAC). Although the incidence of BE has risen rapidly in the West, it is rare in Asia despite a recent increase in the prevalence of gastroesophageal reflux disease. Controversies over the definition of BE are presented because most cases show short-segment BE, especially ultra-short BE, in Asia. Here we review possible risk factors for the development of EAC, particularly possible roles of ethnicity, specialized intestinal metaplasia (SIM), BE length, and environmental factors, such as *Helicobacter pylori* infection and obesity. Additionally, we summarize recent studies on the effect of chemoprevention including proton pump inhibitors, nonsteroidal anti-inflammatory drugs or aspirin in order to reduce the risk of neoplastic progression in BE patients. Although substantial knowledge of risk factors of dysplasia/EAC in BE is shown, the risk for neoplastic development may be influenced by geographic variation, study population, the presence or absence of SIM or dysplasia at baseline, and the small number of BE patients investigated. Recently, the efficiency of surveillance for BE patients has been discussed from the standpoint of cost-effectiveness. It may be too difficult to draw conclusions because no randomized clinical trials of BE surveillance have been performed.

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Introduction

Barrett's esophagus (BE) is a metaplastic condition where the normal squamous epithelium of the lower esophagus is replaced by metaplastic columnar epithelium [1]. From the histological viewpoint, BE includes a combination of three types of columnar epithelia described by Chandrasoma et al. as cardiac, oxyntocardiac, and intestinal [2]. Among these types, intestinal metaplastic mucosa, namely specialized intestinal mucosa (SIM), has been conventionally accepted as the only neoplastic precursor of esophageal adenocarcinoma (EAC) [3–5].

Although there may be a regional variation in the cancer risk among BE patients, it is generally considered that patients with BE have a 30- to 125-fold increase in the risk of developing adenocarcinoma, with an annual incidence rate of approximately 0.5 % [6–8], and monitoring of BE patients for the development of adenocarcinoma is recommended at intervals of 2–3 years [1, 9]. Furthermore, many previous studies have reported that BE often progresses to EAC among male Caucasians in their 60s. Once an individual has been diagnosed as having BE, management strategies such as appropriate surveillance, medical treatment, endoscopic ablative therapy, etc. are needed in order to reduce the risk of progression to EAC.

Here we review the causal factors of EAC and discuss efficient preventive strategies based on the clinical literature, with a focus on original contributions, systematic reviews, and meta-analyses.

Problems in the diagnosis of BE

Argument regarding landmark of esophagogastric junction in the BE definition

The identification of one or more landmarks that define the esophagogastric junction (EGJ) in the clinical diagnosis of BE is of great importance. The clinical diagnosis is based on the endoscopic recognition of red/pink gastric-like mucosa lining the tubular esophagus above the EGJ, which is defined as the most proximal margins of the gastric folds in the West (the Prague C & M criteria) [10–12] and as the lower end of the palisade vessels of the lower esophagus in Japan (the Japanese criteria) [13–15]. In patients with severe atrophic gastritis, particularly Asian and Japanese individuals with *Helicobacter pylori*, the infection—which spreads through the cardia from the antrum-atrophic gastritis—makes it difficult for the oral end of the gastric folds to be used as a marker of the EGJ. However, Kinjo et al. [15] reported that the ratio of endoscopic BE diagnoses using the Japanese criteria was significantly higher than that using the Prague C & M criteria in Japanese atrophic gastritis cases.

Amano et al. [14] showed that the upper end of the gastric folds as used in the Prague C & M criteria may be a more suitable landmark than the palisade vessels for identifying the distal end of the esophagus by endoscopy in Japanese individuals. In their study, however, the coefficient stayed low (κ value = 0.35) although the κ coefficients of reliability in the diagnosis of BE improved markedly after an explanation of the Prague criteria for BE to the endoscopists involved. There is an interesting issue regarding whether American and Japanese endoscopists differ in their recognition of palisade vessels in various ethnic individuals. As a result, American and Japanese endoscopists similarly recognize the distal end of the palisade vessels as the EGJ (κ value = 0.88) [16].

There are a few reports from the West in which the lower end of the palisade vessels is used as the landmark for the EGJ as in Japan [17–19]. An important disadvantage of considering the proximal ends of the gastric folds as the landmark for the EGJ is that the diagnostic concordance is very low, especially in ultra-short (<1 cm in length) and short-segment BE (SSBE), in which is difficult to detect this landmark. Chang et al. [20] demonstrated the utility of the Prague C & M criteria to characterize BE in an ethnic Chinese population even though the BE was ultra-short (<1 cm); however, they did not mention the Japanese criteria. There is another problem in that insufficient extension and inadequate stretching of the lower esophagus, particularly under sedation, may disturb the identification of palisade vessels. Therefore, it is difficult to reach an international conclusion regarding the appropriate criteria to be used to identify the EGJ, Prague or Japanese, because both have drawbacks and advantages.

Clinical problems in the diagnosis of ultra-short BE (<1 cm in length)

Many investigators have pointed out that the endoscopic diagnosis of ultra-short BE is difficult and highly unreliable [12, 21–23]. The overall reliability coefficients for the endoscopic recognition of BE $\geq$1 cm was 0.72, whereas for the endoscopic recognition of BE <1 cm of columnar-lined epithelium (CLE), the coefficient was only 0.22 [12]. One possible reason for the difficulty may be the use of a different definition of the EGJ as discussed above [10–15]. In studies based in the USA, only cases in which SIM was histologically confirmed in CLE were defined as BE, of any length. In contrast, Japanese studies have reported that all CLE identified endoscopically is considered a sign of BE regardless of its length and the presence or absence of SIM on biopsy from CLE [13]. Some studies from Europe included patients without SIM in any length of CLE [24, 25].

However, ultra-short BE does not satisfy either American [9] or British [26] endoscopic requirements for the diagnosis of BE, and several groups have contended that ultra-short BE should therefore not be given the name Barrett's esophagus [9, 19, 27]. In Japan, the term 'BE' is used as a synonym for CLE. When using the distal end of the palisade vessels as the EGJ, most of the Japanese patients in one study (91.7 %, 11 of 12) showed BE <5 mm in length [28], a finding which may cause a diagnostic issue.

Generally, the length of BE is a significant risk factor in the development of dysplasia and cancer, as we will describe below. Although EAC arising from SSBE (including ultra-short BE) has been reported, to the best of our knowledge, no data confirming that ultra-short BE has any increased cancer risk has been found. In an era of growing endoscopic therapy for neoplastic BE, it is important to standardize the BE length. Unfortunately, proximal islands of columnar lining and ultra-short BE (<1 cm) are not included in the updated American College of Gastroenterology (ACG) guidelines (2008) for the diagnosis of BE [9].

SIM (goblet cells) and carcinogenesis

The divergence between the USA [9] and the British Society of Gastroenterology (BSG) guidance [26] relates to intestinalization and the presence of goblet cells on biopsy. The ACG defines BE 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 SIM by biopsy of the tubular esophagus" [9]. The basis for this definition relies mainly on the fact that most of the cases of EAC arise in BE mucosa with SIM, as shown by retrospective cohort studies [29–33]. It has been generally considered, therefore, that SIM in BE is a precancerous condition.

In contrast, the BSG does not require the confirmation of SIM in biopsies from the esophagus to establish the diagnosis of BE [26]. Although the endoscopic requirements are similar to the ACG guidelines, any histological type of columnar epithelium is regarded as acceptable to diagnose BE. The absence of SIM might actually be missed by poor endoscopic sampling due to inadequate numbers of biopsy specimens, thus supporting the BSG viewpoint that the demonstration of CLE in an appropriate endoscopic setting is sufficient for the diagnosis of BE. Crucial questions remain such as 'Is SIM the premalignant phenotype?' and 'Is it therefore the most significant feature for the diagnosis of BE?' [34]

The updated practice guidelines published in 2011 by the American Gastrointestinal Association (AGA) state that intestinal-type epithelium (SIM) is the only type of esophageal columnar epithelium that clearly predisposes a patient to malignancy [35]. In a subgroup analysis by status in BE, the incidence of EAC in patients with SIM in BE at an index biopsy was 0.23 % patient-years (pyrs) (95 % confidence interval [CI] 0.18–0.29 % per year), and the risk of cancer was significantly higher in patients with SIM than in patients whose first biopsies did not show SIM (0.04 % per year, 95 % CI 0.02–0.08 % per year) [43].

However, it has been reported that cardia-type epithelium may not be normal, and a pair of studies revealed molecular abnormalities in such epithelium that are similar to those found in SIM [36, 37]. Liu et al. [36] reported that patients with esophageal columnar metaplasia, but without SIM (goblet cells), showed DNA content abnormalities statistically similar to metaplastic columnar epithelium with SIM. In an interesting clinical study by Takubo et al. [38], it was revealed that 71 % of BE patients had cardia-type epithelium, not SIM, found adjacent to tiny EAC, and 57 % had no SIM as detected in the specimen by endoscopic resection. Other studies indicated a similar finding, i.e., that non-SIM BE mucosa has the same cancer risk as that of intestinal-type mucosa [39–41].

Vieth et al. [42] searched for SIM associated with EAC and found that the incidence of SIM in the surrounding mucosa of EAC ranges from 30−100 %. The risk of dysplasia or EAC is not necessarily related to the presence or absence of SIM, because the detection of SIM is strongly associated with the number of biopsy specimens obtained [40, 43]. Taking into account these results, future classifications of BE might not require the presence of SIM, a policy which would increase the number of patients considered to be at risk.

Is the presence of SIM associated with a risk of developing EAC? The great majority of studies on the risk of cancer in BE have included patients with SIM either primarily or exclusively [44]. Although recent data suggest that cardia-type epithelium may well predispose to malignancy, the magnitude of that risk remains clear [35, 45], and thus the AGA does not recommend use of the term "BE" for patients with cardia-type epithelium [35].

Risk factors for EAC or dysplasia

Incidence of EAC or dysplasia in BE patients

BE is well recognized as a premalignant condition, and the incidence of EAC arising in individuals with BE is increasing in the West [46–48]. Surveillance endoscopy has thus been recommended for BE patients with the aim of detecting dysplasia and early cancer and subsequently improving survival [9]. Recommended surveillance intervals provided in the AGA medical position statement suggest intervals of 3–5 years for patients who have no dysplasia, 6–12 months for those with low-grade dysplasia (LGD), and every 3 months for patients with high-grade dysplasia (HGD) who receive no ablation therapy; however, it is a weak recommendation accompanied by low-quality evidence [35]. In Asia including Japan, although the incidence of gastroesophageal reflux disease (GERD) has been increasing in recent years [49–53], EAC remains rare and has not increased [54–57].

The true annual incidence of EAC in BE patients is unclear because cohort studies have shown considerable variation, ranging from 0.2−3.5 % per year [58, 59]. As Sikkema et al. [60] pointed out, however, these rates could have been overestimated as a result of publication bias in published BE surveillance studies, with evidence of a selective publication of small studies with high cancer incidence rates [44]. The rates may also have been affected by the difference in study populations, i.e., general population versus hospital-based studies. To the best of our knowledge, there have been no randomized controlled trials (RCTs) comparing surveillance with no surveillance in BE patients. Since RCTs comparing surveillance with non-surveillance in BE patients in terms of cancer-related deaths are not likely to be conducted, a meta-analysis of both the risk of cancer and cancer-related deaths in BE could provide another way to address the question of true annual incidence of EAC in BE patients [60].

If RCTs are needed to clarify the incidence of EAC in BE patients, the RCTs must overcome overwhelming barriers in terms of both practical difficulties and ethical challenges [61]. Several systematic reviews and meta-analyses on the EAC risk in BE patients [60, 62–66] are summarized in Table 1. Among these studies, the rate of progression in BE without dysplasia at baseline to EAC is low, ranging from 0.33 % (95 % CI 0.28–0.38 %) to 0.598 % (95 % CI 0.505–0.691 %) annually [65, 66]. Bhat et al. [43] reported the risk of malignant progression in BE patients in Northern Ireland, in which they studied the incidence of not only EAC but also gastric cardia cancer or BE with dysplasia. According to their results, when calculating the incidence of only EAC, the incidence of EAC was 0.16 % pyrs in the whole cohort, 0.10 % pyrs in the nondysplastic BE patient group, and 0.92 % pyrs in the LGD group. In contrast, the pooled annual incidence of EAC in the patients with dysplasia at baseline, LGD, or HGD ranged from 2.8/1,000−6.3/1,000 pyrs. However, there are some problems in these data such as (1) publication bias, (2) it was not reported whether the authors excluded patients with dysplasia such as LGD or HGD at baseline, and (3) it was not reported whether patients had documented SIM histologically.

Although there are several studies showing the presence of dysplasia as a risk factor for the development of EAC as mentioned above, a meta-regression analysis by Thomas et al. [63] showed that the presence of LGD on an index biopsy had no significant effect on the cancer incidence rates. This may be explained by the wide intra- and inter-observer variability in the reporting of LGD, even among expert pathologists. The number of pathologists reporting histology was not clear from the studies. It is therefore possible that several patients with LGD on index biopsy may not have had dysplasia at all. In addition, difficulties in the histological diagnosis for HGD or EAC may occur when biopsy samples are evaluated, and thus patients with confirmed HGD at baseline should be excluded from the study.

Table 1 Incidence of esophageal adenocarcinoma and high-grade dysplasia among patients with Barrett's esophagus

References	Year	Incidence rate/1,000 pyrs (95 % CI)		Definition of BE	On initial endoscopy	Publication bias
		EAC	EAC and HGD			
Chang et al. [62]	2007	Controlled studies (RCT and cohort study) 4.8 (1.7–11.1) in surgically treated group 6.5 (2.6–13.8) in medically treated group	Not specified	Histologically SIM	Including LGD and HGD	Heterogeneity in surgically treated group
Thomas et al. [63]	2007	7 (6–9) [7 (4–12) in the UK, 7 (4–9) in the US, 8 (5–12) in Europe, and 5 (1–25) in Australia and New Zealand]	9 (7–11) [9 (5–16) in the UK, 8 (6–11) in USA, 11 (7–17) in Europe, and 5 (1–25) in Australia and New Zealand]	Endoscopically or histologically SIM	Including LGD	No publication bias in the UK and EU studies but in the USA studies
Yousef et al. [64]	2008	4.1 (3.1–5.5) [7.0 (4.2–11.5) in the UK, 6.4 (4.1–9.8) in the US, and 5.6 (3.7–8.5) in other Europe]	9.1 (5.9–13.8) (with heterogeneity)	Endoscopically or histologically SIM, mainly histologically	Including LGD but excluded HGD at baseline, and early incident cancer and HGD	Not significant
Wani et al. [65]	2009	5.98 (5.05–6.91) in nondysplastic BE 16.98 (13.1–20.85) in LGD 65.8 % (49.7–81.9) in HGD (with heterogeneity)	Not specified	Histologically SIM	Separately evaluated in nondysplastic BE, LGD, and HGD	The incidence of EAC in only patients with LGD
Sikkema et al. [60]	2010	6.3 (4.7–8.4) (with heterogeneity) [6.3 (4.2–9.3) in the UK, 6.5 (3.4–12.4) in the USA, 5.6 (3.5–9.2) in other Europe, and 6.5 (3.5–12.2) in Australia]	10.2 (7.5–14.0) (with heterogeneity) [13.0 (7.4–22.8) in the UK, 11.0 (6.9–17.5) in the USA, 7.3 (3.6–15.0) in other Europe, and 6.5 (3.5–12.2) in Australia]	Histologically SIM or columnar lined esophagus	Including LGD and HGD	Present among studies from the USA, but not from the UK and other studies
Desai et al. [66]	2012	3.3 (2.8–3.8)	Not specified	Histologically SIM	Nondysplastic BE	Not significant

EAC esophageal adenocarcinoma, *HGD* high-grade dysplasia, *LGD* low-grade dysplasia, *BE* Barrett's esophagus, *RCT* randomized controlled trial, *SIM* specialized intestinal metaplasia, *CI* confidence intervals, *pyrs* patient-years

It may also be possible that the presence or absence of SIM at baseline influences the incidence of EAC during follow-up. Although it is believed that the presence of SIM in BE raises the cancer risk, it is now clear that EAC can occur without SIM being detected. In an analysis by Bhat et al. [43], the incidence of EAC in patients with SIM in BE at index biopsy was 0.23 % pyrs (95 % CI 0.18–0.29 % per year), and the risk of cancer was significantly higher in patients with SIM compared to patients whose first biopsies did not show SIM (0.04 % per year, 95 % CI 0.02–0.08 % per year).

More recently, a large nationwide population-based cohort study in the Netherlands involving BE patients with histologically confirmed SIM revealed that the annual risk of EAC was 0.4 %, and after excluding HGD/EAC cases detected within 1 year after BE diagnosis, the incidence rates were 4.3/1,000 pyrs (95 % CI 3.4–5.5) for EAC and 5.8/1,000 pyrs (95 % CI 4.6–7.0) for HGD/EAC combined [67]. LGD at diagnosis was found to be an independent predictor of malignant progression in that study. A similar population-based cohort study in Denmark reported that the incidence of EAC and HGD among patients with BE, with or without LGD was 0.12 % pyrs (95 % CI 0.9–1.5) and 0.19 % pyrs (95 % CI 1.6–2.3), respectively; these values were lower than previously reported data. The relative risks of EAC and HGD, i.e., 11.3 (95 % CI 8.8–14.4) and 65.3 (95 % CI 53.5–79.0), were as high among patients with BE as in the general population, but significantly lower than those found in earlier studies [68]. These results may call into question the cost-effectiveness of generalized BE surveillance programs in the West. There have been few prospective cohort studies on the incidence of EAC or dysplasia in Asia and Japan.

Geographic difference of cancer risk

A geographic difference in EAC incidence in BE between the UK and the USA was reported, with the incidence in the UK being twice that of the USA [69]. However, in the meta-analysis by Thomas et al. [63], the incidence in the UK (0.7 % per year) was the same as the incidence in the USA (0.7 % per year), providing no support for the hypothesis of geographic variation in cancer incidence. However, Thomas et al. mentioned that this result may be confounded by the inclusion of two large UK studies. The exclusion of these studies for the reasons stated above would support published figures showing a higher cancer incidence in the UK compared to the USA. A geographic variation in BE cancer risk has been suggested by another group [46]. Very small differences in the EAC incidence were reported between different geographic regions, with only a slightly higher EAC incidence in the USA and UK compared to other European countries, which is in line with other studies [63, 64]. The incidence in Australia and New Zealand was slightly lower than that in the USA and Europe including the UK [63].

BE length and carcinogenesis

It has been thought that patients with long-segment BE (LSBE ≥3 cm BE length) have a much higher risk of developing EAC than individuals in the general population [8, 70–72]. Avidan et al. [73] reported that each centimetre of elongation of BE carried with it a 17 % increase in the risk of developing HGD or EAC. A follow-up study by Weston et al. [74] showed that the incidence of EAC was significantly lower in patients with SSBE (<3 cm in length) than in those with LSBE (0 vs 7.5 %). Avidan et al. also reported the incidence of the development of multifocal HGD/EAC as 23.1 % for patients with >6 cm of BE and 3.6 % for BE lengths of >2 and ≤6 cm. According to a review by Caygill et al. [61], the risk of overall or incident cancers was greater for SSBE than for LSBE (3–6 cm) but the greatest risk is for segments >6 cm. Taken together, these results indicate that dysplasia and EAC can occur in BE of all lengths.

Among three meta-analyses (Table 2), two demonstrated that the risk for EAC was lower in patients with SSBE than in those with LSBE [63, 66], but the other did not show the trend [64]. There have been several reports on the incidence of EAC in patients with SSBE [75–79], but relatively few patients with SSBE were included in these meta-analyses; overall, they accounted for <10 % of the total number of pyrs

Table 2 Association between the length of Barrett's esophagus and cancer risk

References	Year	Incidence of EAC (95 % CI)		Publication bias
		SSBE	LSBE	
Thomas et al. [63]	2007	OR 0.55 (0.19–1.5) (EAC risk in patients with SSBE compared to LSBE)		NS (except the USA studies)
Yousef et al. [64]	2008	6.1/1,000 pyrs (3.1–12.2)	6.7/1,000 pyrs (5.2–8.6)	NS
Desai et al. [66]	2012	1.9/1,000 pyrs (0.8–3.4)		NS

EAC esophageal adenocarcinoma, *SSBE* short-segment Barrett's esophagus, *LSBE* long-segment Barrett's esophagus, *NS* not significant, *CI* confidence intervals, *OR* odds ratio, *pyrs* patient-years of follow-up. Desai et al. [66] revealed that the risk of EAC among patients with SSBE is notably lower than the pooled estimate for all patients with BE. The sub-analysis by Thomas et al. [63] showed significantly greater lengths of BE in patients who developed cancer compared to those who did not, while there was a non-significant trend toward reduction in the risk of developing EAC in the patients with SSBE compared to conventional BE (odds ratio [OR] 0.55, 95 % CI 0.19–1.5), although this analysis was based on data from a small number of studies. These data appear to support the previous contention that patients with longer BE are at higher risk of developing EAC [80].

Horwhat et al. [18] also showed that the incidence density for EAC/dysplasia in an LSBE cohort was 7.7 % pyrs, whereas the incidence density of dysplasia was 1.8 % pyrs in the SSBE cohort. In contrast, another meta-analysis by Yousef et al. [64] found no difference in the pooled estimate of overall cancer incidence between patients with LSBE (0.67 % pyrs) and those with SSBE (0.61 % pyrs). Rudolph et al. [81] reported that the risk for EAC in patients with SSBE was not substantially lower than that in patients with LSBE, and when patients with HGD at baseline were excluded, a nonsignificant trend was observed. However, their study was not among those analyzed in the two meta-analyses [63, 66] described above. The presence or absence of dysplasia at baseline is likely to affect the results, and all patients with any degree of dysplasia at baseline should be excluded from analysis. Taken together, these results indicate that dysplasia and EAC can occur in patients with BE of any length, whereas the risk may be associated with BE length.

A large cohort multicenter study from the USA indicated that compared to non-progressors, patients who developed HGD or EAC had longer BE (6.1 vs 3.5 cm; $p < 0.001$), and a logistic regression analysis showed a 28 % increase in the risk of HGD or EAC for every 1 cm increase in BE length ($p = 0.01$) [82]. That study also revealed that the annual incidence of HGD or EAC was 0.67 %/year during the mean follow-up period (5.5 years).

H. pylori infection and carcinogenesis

There are many studies on the relationship between *H. pylori* and GERD. Although the association is complex, it has generally been considered that *H. pylori* infection, with the cytotoxin-associated gene A (*cagA*)-positive strain, is inversely associated with the risk of GERD, and thus *H. pylori* may have a protective role against GERD. In contrast, several meta-analyses have indicated that *H. pylori* eradication does not seem to aggravate GERD or increase the rate of new development of GERD.

The association between *H. pylori* infection and BE or BE-associated EAC is controversial. A meta-analysis by Rokkas et al. [83] showed a significant inverse relationship between *H. pylori* infection and both EAC (pooled OR 0.52, 95 % CI 0.37–0.73, $p < 0.001$) and BE (pooled OR 0.64, 95 % CI 0.43–0.94, $p < 0.025$), which might suggest a protective role of the infection in these entities. However, their meta-analysis included patients with GERD, functional dyspepsia and a variety of non-BE diseases as controls, which would not accurately reflect the true effect size of *H. pylori* infection in BE versus healthy controls.

There are various reports on the association between *H. pylori* and BE. According to a meta-analysis by Fischbach et al. [85], *H. pylori*, especially the *cagA*-positive strain of *H. pylori*, tended to be protective for BE in most studies; however, there was obvious heterogeneity across the studies. The effect of *H. pylori* on BE varied by geographic location and in the presence of selection and information biases. When four studies with obvious selection and information bias were excluded, a protective effect of *H. pylori* on BE was found (relative risk 0.46, 95 % CI 0.35–0.60). Wang et al. [86] reported that there was no significant difference in the overall prevalence of *H. pylori* infection between BE patients and controls (42.9 vs 43.9 %, OR 0.74, 95 % CI 0.40–1.37, $p = 0.34$), but with significant heterogeneity. A subgroup analysis showed that the prevalence of *H. pylori* infection was significantly lower in the BE group compared to the endoscopically normal healthy controls (23.1 vs 42.7 %, OR 0.50, 95 % CI 0.27–0.93, $p = 0.03$) with significant heterogeneity observed between studies.

In contrast, *H. pylori* infection was significantly increased in BE patients in a few studies using healthy blood donors without endoscopic examination as 'normal controls' (71.2 vs 48.1 %, OR 2.21, 95 % CI 1.07–4.55) in a meta-analysis. Thrift et al. [87] reported a population-based case–control study which found that *H. pylori* infection was inversely associated with BE, whereas there was some variation in the magnitude of risk estimates across strata of age, gender, reflux symptoms, and use of proton pump inhibitors (PPIs) or H_2-receptor antagonists (H_2RAs Further studies are needed to test this association, and the studies should enroll patients prospectively to ensure standard BE diagnostic methods, *H. pylori* detection methods, and overall high study quality.

In contrast, in a rat model of chronic gastroesophageal reflux, when *H. pylori* colonized in the esophagus, the bacteria increased the severity of esophageal inflammation and the incidence of BE and EAC [84].

It may be true that there is marked geographic heterogeneity in the association between *H. pylori* and BE [86, 88, 89]. As found in other studies, a study from Japan showed that *H. pylori* infection may play a protective role in the development of BE (especially LSBE), although the number of patients evaluated was limited [90]. The same group proposed that the preservation of gastric acid secretion might be important for the development of adenocarcinoma at the EGJ (including EAC) in Japanese people, irrespective of the *H. pylori* infection status [91]. Namely, there may be two distinct types of cancer at the EGJ—EAC (BE cancer) associated with high gastric acid secretion and reflux of gastric acid into the esophagus and EGJ adenocarcinoma (non-BE cancer) resembling distal gastric cancer associated with gastric atrophy and low gastric acid secretion [92, 93].

Nakajima and Hattori conducted a systematic review and reported that even for patients with accompanying BE, the expected incidence of either gastric cancer or EAC with persistent infection was higher than that of EAC after *H. pylori* eradication, and they hypothesized that if the treatment of *H. pylori* infection lowers the incidence of gastric cancer, it should be recommended for patients with corpus atrophy at all ages irrespective of the presence of BE, especially in populations with a high prevalence of gastric cancer [94].

Obesity and carcinogenesis

It is well known that simple obesity as measured by body mass index (BMI) may be an independent risk factor for GERD, reflux esophagitis (RE), BE, and EAC [95, 96]. In contrast, waist circumference (WC) rather than BMI is associated with esophageal acid exposure, with larger WCs leading to a risk of GERD and BE [97]. Recent epidemiological studies showed that WC and the waist-to-hip ratio (WHR), both of which are associated with increased abdominal fat, are risk factors for BE independent of the BMI, with the association between BMI and BE no longer observed after adjustment for WC or WHR [98, 99].

El-Serag et al. [100] estimated that each 10 cm^2 increase in visceral adipose tissue (VAT), which was calculated from CT scan images, was associated with a 9 % increase in the risk of BE, and VAT remained independently associated with BE in the model adjusted for BMI. However, there has been little study of the correlation between obesity and BE in Japan. Akiyama et al. [101] reported a retrospective study on the positive association between VAT and BE in Japanese patients with non-alcoholic fatty liver disease, but the strength of the risk of BE was very weak (OR 1.0074, 95 % CI 1.0001–1.0147, $p = 0.0472$).

It thus remains controversial whether obesity is actually an independent risk factor for BE in a Japanese population. Because the prevalence of abdominal obesity varies by gender and ethnicity [102], it is possible that body fat distribution may predict the risk of not only BE but also EAC better than total obesity. It is well known that the prevalence of GERD and its complications, such as RE and BE, may vary substantially by gender and ethnicity [103–105]. Many studies have shown that obesity was associated with an increased risk for EAC [106–117]. All of these studies showed a positive association between being overweight (BMI >25 kg/m^2) or obese (BMI >30 kg/m^2) and the development of EAC (Table 3). These studies indicated that obesity was associated with an approximate 1.5- to 2.5-fold increase in the risk of EAC compared to normal BMI values.

The FINBAR (Factors Influencing the Barrett's Adenocarcinoma Relationship) study [116] comparing risk factors for both BE and EAC showed that patients with a high BMI were significantly more likely to develop EAC but not BE (with SIM and ≥3 cm in length), thus demonstrating important differences between BE and EAC in their association with BMI. This result indicates that the pathogenesis of EAC may be different from that of GERD including BE [113]. In the FINBAR study, no relationship was observed between WHR and EAC (OR 0.80, 95 % CI 0.50–1.28) or between WHR and BE (OR 1.09, 95 % CI 0.68–1.73), but the reasons for these results were not clear [116]. The results of observational studies may be influenced by unmeasured confounders. Some factors, such as physical activity and dietary composition, may be related to BMI and were not routinely adjusted for in all studies; however, studies that included estimates with and without adjustment for these variables did not show a substantial influence of these factors on the risk estimates [109].

When a tumor is located at the EGJ, especially at the advanced stage, the diagnosis of the cancer may be difficult; possible diagnoses include EAC alone, gastric cardiac cancer alone, or the combination of EAC with cardiac cancer [118]. Two meta-analyses examined the association between obesity and cancer divided into two types, EAC and cardiac cancer of the stomach [96, 118]. Both meta-analyses revealed a positive association between high BMI and the risk for EAC, and possibly the risk for cardiac cancer because of the heterogeneous results.

Neoplastic prevention

PPIs and chemoprevention in BE

For GERD and BE patients without dysplasia, it is debated which therapy, medical or surgical, is appropriate for the prevention of EAC. One advantage of anti-reflux surgery is the creation of a mechanical valve which prevents all forms of gastroesophageal reflux. On the other hand, PPIs and H_2RAs reduce the acidity of gastric secretions but do not prevent nonacidic reflux [119], which has been implicated in carcinogenesis [120]. These observations have fueled speculation that surgical anti-reflux procedures may prevent the development of EAC more effectively than

Table 3 Association between esophageal adenocarcinoma and body mass index

References	Year	Country	Design	BMI categories	Adjusted odds ratio (95 % CI)	BMI reference	Adjustments
Brown et al. [106]	1995	USA	Case–control study	25.1–26.6	1.2 (0.6–2.3) in white men	<23.1	Age, area, smoking, liquor use, and income
				>26.6	3.1 (1.8–5.3) in white men		
Vaughan et al. [107]	1995	USA	Population-based case–control study	Percentile 90–100 %	2.5 (1.2–5.0)		Age, gender, education, race, cigarette use, and alcohol consumption
Chow et al. [108]	1998	USA	Population-based case–control study	Males 25.09–27.31	2.0 (1.3–3.3)	Males <23.12	Geographic location, age, sex, race, cigarette smoking, and respondent status
				Females 24.13–27.43		Females <21.95	
				Males ≥27.32	2.9 (1.8–4.7)		
				Females ≥27.44			
Lagergren et al. [109]	2001	Sweden	Population-based case–control study	Males 22.3–23.9	2.2 (1.0–4.7)	Males <22.3	Age, sex, race, tobacco smoking, alcohol use, socioeconomic status, reflux symptoms, intake of fruit and vegetables, energy intake, and physical activity
				Females 21.1–22.4		Females <21.1	
				Males 24.0–25.5	3.8 (1.9–7.7)		
				Females 22.5–24.2			
				Males >25.6	7.6 (3.8–15.2)		
				Females >24.2			
Wu et al. [110]	2001	USA	Population-based case–control study	Males >25 to ≤28	1.34 (0.9–2.1)	Males ≤23	Smoking status, age, sex, race, birthplace, and education
				Females >25 to ≤28.25		Females ≤22	
				Males >28	1.91 (1.3–2.9)		
				Females >28.25			
Engeland et al. [112]	2004	Norway	Retrospective cohort study	25.0–29.9 in men	RR 1.80 (1.48–2.19)	18.5–24.9	Age and year of birth
				25.0–29.9 in women	RR 1.64 (1.08–2.49)		
				≥30.0 in men	RR 2.58 (1.81–3.68)		
				≥30.0 in women	RR 2.06 (1.25–3.39)		
Hampel et al. [96]	2005		Meta-analysis	≥25	1.52 (1.147–2.009)		
				>30	2.78 (1.850–4.164)		
Lindblad et al. [113]	2005	UK	Population-based case–control study	25–29 in men	1.87 (1.25–2.80)	20–24	Adjusted for age, calendar year, smoking alcohol consumption and reflux
				25–29 in women	1.08 (0.50–2.33)		
				≥30 in men	1.76 (1.03–3.02)		
				≥30 in women	2.13 (0.97–4.71)		
Samanic et al. [114]	2006	Sweden (men)	Prospective cohort study	25.0–29.9	RR 1.58 (0.98–2.53)	18.5–24.9	Attained age (10-year intervals) and calendar year (5-year intervals), and smoking status, and relative to normal weight subjects
				>30.0	RR 2.72 (1.33–5.55)		

Table 3 continued

References	Year	Country	Design	BMI categories	Adjusted odds ratio (95 % CI)	BMI reference	Adjustments
Kubo and Corley [118]	2006		Meta-analysis	25–28 in men	1.8 (1.5–2.2)	≥18.5 to <25	
				25–28 in women	1.5 (1.1–2.2)		
				≥28 in men	2.4 (1.9–3.2)		
				≥28 in women	2.1 (1.4–3.2)		
Anderson et al. [116]	2007	Ireland	Population-based case–control study	25.0–28.1 (5 years in tertiles)	1.74 (0.66–1.97)		Sex, age at interview date, smoking status, alcohol intake (g), year of full-time education and job type
				>28.1 (5 years in tertiles)	2.69 (1.62–4.467)		
Abnet et al. [115]	2008	USA	Prospective cohort study	≥25 to <30	HR 1.65 (1.26–2.18)	≥18.5 to <25	Age, sex, cigarette smoking, alcohol consumption, education, fruit and vegetable consumption and physical activity
				≥30 to <35	HR 1.91 (1.38–2.66)		
				≥35	HR 2.27 (1.44–3.59)		

BMI body mass index, *CI* confidence intervals, *RR* relative risk, *HR* hazard ratio

medical anti-secretory therapy. A systematic review by Chang et al. [62] showed that the incidence rate of EAC was 2.8/1,000 pyrs in surgically treated patients and 6.3/1,000 pyrs in medically treated patients ($p = 0.034$). When controlled studies were evaluated, however, the incidence rates were 4.8/1,000 and 6.5/1,000 pyrs in surgical and medical patients, respectively ($p = 0.320$). The likely reason for the discrepancy is the heterogeneity in incidence rates in surgically treated patients between the controlled studies and the case series ($p = 0.014$). These results thus indicate that anti-reflux surgery in patients with BE does not prevent the development of EAC appreciably more than medical therapy.

There is some evidence to suggest that PPIs can lead to a partial regression of BE [121, 122] and delay the progression to dysplasia or EAC [123, 124]. Accordingly, the increasing use of PPIs since the late 1980s might have contributed to the slight drop in the incidence of EAC over the past several decades. Moreover, since the 1990s, several studies using varying doses of PPIs reported partial regression or the development of squamous islands [121, 125–128], while circumferential regression of the columnarized segment was rare.

Epidemiological studies have shown that the long-term use of PPIs is associated with lower rates of dysplasia and EAC in patients with BE [122, 124, 129–131], except for one study [132]. In two other studies, the early use of a PPIs after the diagnosis of BE was associated with a decreased risk of developing dysplasia or EAC [122, 129] (Table 4). The available data are insufficient to draw any definite conclusions [133, 134]. As the AGA noted [45], the evidence to support potent acid suppression with PPIs as a chemopreventive strategy in BE is largely indirect. A number of observational studies have found an inverse correlation between the long-term use of PPIs and the incidence of dysplasia and EAC in patients with BE [122–124, 135]. Some prospective clinical studies have shown that PPI therapy is associated with a decrease in proliferation markers, a potentially cancer-protective effect, in biopsy specimens of Barrett's metaplasia [136–138]. However, prospective clinical studies have yet to prove that PPI therapy can prevent the development of dysplasia and its progression in BE, and thus the quality of evidence of the association is low [35]. Indeed, García Rodríguez et al. [130] reported that individuals with long-term use of PPIs or H_2RAs for 'esophageal' indication, i.e., reflux symptoms, esophagitis, BE, or hiatal hernia, showed a five-fold increased risk of EAC (OR 5.42, 95 % CI 3.13–9.39).

Taken together, these studies suggest that the use of PPIs may prevent the development of dysplasia or EAC in BE patients, although it could not completely eliminate the risk of neoplastic progression. A large-scale, long-term, multicenter randomized controlled trial is needed to explore the usefulness of PPIs as a chemopreventive agent for dysplasia or EAC.

Aspirin/nonsteroidal anti-inflammatory drugs and chemoprevention

A meta-analysis showed that the use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) was protective against EAC (OR 0.67, 95 % CI 0.51–0.87) [139]. Two prospective studies also showed that NSAID use reduced the risk of neoplastic progression in patients with BE [140, 141]. A study from Australia showed that patients who took aspirin at least weekly had significantly lower risks of

Table 4 Use of proton pump inhibitors and risk of esophageal adenocarcinoma or high-grade dysplasia

References	Year	Design	Histology subtypes of outcome	Medication use	Adjusted odds ratio (95 % CI)	Adjustments
El-Serag et al. [122]	2004	Prospective study	Dysplasia	After BE diagnosis	HR 0.25 (0.13–0.47)	BE length, year of BE diagnosis, age at time of diagnosis, gender and race
García Rodríguez et al. [130]	2006	Population-based nested case–control study	EAC	Current use; within 1 year before the index date	1.51 (0.91–2.50)	Age, sex, calendar year, smoking, alcohol consumption, and body mass index
				Past use; the last use before the index date	0.81 (0.33–1.99)	
de Jonge et al. [131]	2006	Hospital-based case–control study	EAC	<6 months	2.7 (0.7–11)	Age, gender, educational level, smoking status, alcohol use, and reflux symptoms
				>6 months	0.04 (0.02–0.09)	
Hillman et al. [129]	2008	Retrospective/prospective cohort study	LGD or a macroscopic marker	After BE diagnosis	IDR 3.4 (1.98–5.85)	Age, gender and year of diagnosis
Nguyen et al. [124]	2009	Retrospective observational study	HGD/EAC	After BE diagnosis	HR 0.39 (0.19–0.80)	Age, gender and BE length
				Before or after BE diagnosis	HR 0.38 (0.18–0.77)	
Nguyen et al. [132]	2010	Nested case–control study	EAC	After BE diagnosis and ending 3 months before the EAC diagnosis	IDR 1.50 (0.61–3.66)	Race, outpatient encounters, noncancer disease comorbidity index, VA priority level, and filled prescriptions of NSAID or statin medication categories

A macroscopic marker indicates endoscopic finding such as severe esophagitis, stricture, nodularity or Barrett's ulcer

EAC esophageal adenocarcinoma, *HGD* high-grade dysplasia, *LGD* low-grade dysplasia, *BE* Barrett's esophagus, *CI* confidence intervals, *HR* hazard ratio, *IDR* incidence density ratio, *VA* Veterans' Affairs, *NSAID* nonsteroidal anti-inflammatory drug

EAC (OR 0.48, 95 % CI 0.32–0.72), and other NSAIDs were also associated with reduced risks of EAC (OR 0.74, 95 % CI 0.51–1.08), particularly among patients with frequent GERD symptoms [142].

In a nested case–control study of individuals with BE, an inverse association was found between filled NSAID/aspirin prescriptions and EAC, which remained significant when adjusted for PPI prescription, among other factors (incidence density ratio 0.64, 95 % CI 0.42–0.97) [132]. Similarly, a recent meta-analysis demonstrated that compared to nonusers, individuals who have used aspirin or nonaspirin NSAIDs had a significantly reduced risk of EAC. The highest levels of frequency (daily or more frequently) and duration ($\geq$10 years) of NSAID use were associated with an approximate 40 % reduction in the risk of EAC, with ORs of 0.56 (95 % CI 0.43–0.73, $p = 0.001$) and 0.63 (95 % CI 0.45–0.90, $p_{\text{trend}} = 0.04$), respectively [143].

In contrast, the 'Chemoprevention for Barrett's Esophagus Trial (CBET)', a phase IIb multicenter trial assessing the efficacy of the selective COX-2 inhibitor celecoxib in patients with BE showed that the use of celecoxib for 48 weeks did not prevent the progression of BE [144]. Similar results were obtained in a large retrospective study of the UK National Barrett's Oesophagus Registry database, in which no protection from progression to LGD, HGD or EAC was found with the use of aspirin (typically 75 mg/day) [145].

Nguyen et al. [124] showed only a nonsignificant trend toward a lower incidence of HGD or cancer associated with NSAID/aspirin prescriptions. In another study, patients with EAC used NSAIDs/aspirin more frequently compared to the controls (OR 1.8, 95 % CI 1.1–3.2) [131]. In contrast, celecoxib treatment attenuated the incidence of EAC by inhibiting COX-2 expression in an animal model [84]. The possible beneficial role of NSAIDs/aspirin needs to be further examined, with special attention to the progression from BE to cancer.

Falk et al. [146] reported an interesting study in which the combination use of esomeprazole and the short-term administration of higher doses of aspirin, but not lower doses or no aspirin, significantly reduced the tissue concentrations of prostaglandin E2 in patients with BE with either no dysplasia or LGD. These data support the further evaluation of higher doses of aspirin and esomeprazole to prevent EAC in these patients. In addition, a large ongoing clinical trial, the AspECT (Aspirin Esomeprazole Chemoprevention Trial) trial, was designed to evaluate the effects of esomeprazole and/or aspirin on the rate of progression to HGD or EAC in patients with BE [147]. This ongoing study may provide an answer to the above questions.

Taken together with previous studies, it is apparent that NSAID intake may be associated with a significant reduction in the risk of EAC, but it remains unclear whether this possible benefit is a result of the reduced risk of BE, reduced risk of cancer in BE, or both.

Ablation therapy for dysplasia and EAC

To date, endoscopic ablation therapy has been recommended as a strategy to eradicate HGD. A meta-analysis and systematic review by Wani et al. [65] demonstrated that for BE patients who underwent ablative therapies, the weighted-average incidence rates (WIRs) for cancer were 1.63/1,000 pyrs (95 % CI 0.07–3.34) for nondysplastic BE, 1.58/1,000 pyrs (95 % CI 0.66–3.84) for LGD, and 16.76/1,000 pyrs (95 % CI 10.6–22.9) for HGD patients. In this meta-analysis, the WIR for cancer was higher for nondysplastic BE than for LGD patients undergoing ablation. This most likely represents a statistical aberrancy due to the smaller sample sizes in the LGD studies. In a multicenter, sham-controlled trial, radio frequency ablation was associated with a high rate of complete eradication of both dysplasia and intestinal metaplasia and a reduced risk of disease progression in patients with dysplastic BE [148].

The persistence of underlying SIM (superficial and buried under the neo-squamous epithelium) after ablation is a problem that cannot be ignored. This has been reported in 0–44 % of cases, and the long-term follow-up of successfully treated patients showed recurrence of SIM ranging from 0−68 % [149]. This is not specific for the type of ablative therapy, and a number of investigators using various modes of ablative therapy have reported this finding [150–156]. Residual SIM carries with it the potential to progress to dysplasia/EAC, but the magnitude of this risk is not well characterized [155, 156]. Consensus recommendations based on the medical literature that clinicians could use to manage patients with BE and LGD, HGD, or early-stage EAC have been reported [157]. When treating patients with BE-associated dysplasia or EAC, we should consult these evidence-based consensus statements for the management of such patients.

Surveillance of BE and perspectives

In an examination of cause-specific mortality in BE patients, the total number of patients died from EAC was small and the remaining died due to other causes, including cardiovascular disease, pulmonary disease and other malignancies [60].

To date, we know of no randomized controlled trials of BE surveillance that have been published; however, several authors have used mathematical models to explore the cost-effectiveness of surveillance [158–160]. Despite different modeling approaches and the application of different costs, these studies confirm that the cost-effectiveness of surveillance is crucially dependent on the incidence of EAC. On the basis of costs in the USA, Provenzale et al. [158] concluded that, for a cancer risk of 5 per 1,000 pyrs, surveillance every 4 years was indicated and, if the risk was 0.4 percent per year, surveillance every 5 years was the only strategy to increase a patient's quality of life. With regard to modeling surveillance from a UK perspective, Garside et al. [160] concluded that, at a cancer risk equivalent to 0.5 percent per year, no surveillance costs less and results in a better quality of life than surveillance, irrespective of the surveillance interval used. The estimates of cancer incidence obtained from this systematic review are close to those used in these models and clearly indicate that the cost-effectiveness of Barrett's surveillance is questionable unless it can be targeted to those BE patients who are at the highest risk of cancer. Therefore, this undermines the cost-effectiveness of BE surveillance and supports the search for valid risk stratification tools to identify the minority of patients who are likely to benefit from surveillance [60, 64]. Hence, surveillance strategies for patients with nondysplastic BE, particularly those with short segments, may need to be reconsidered [66]. In the future, chemoprevention may be needed more than surveillance.

Not everyone with CLE has a similar risk of developing EAC, and much work has been done to identify factors that increase the risk. The risk factors which have been identified are broadly divisible into demographic, pathophysiological, environmental, histopathological and molecular genetics [61].

The question remains as to whether endoscopic surveillance should be recommended in SSBE as well as LSBE. Commonly, the overall incidence rate of colorectal cancers in ulcerative colitis (UC) has been reported to be 3/1,000 pyrs duration (95 % CI 2/1,000–4/1,000) [161]. The cancer incidence rate for SSBE may be higher than the cancer incidence in UC, where surveillance is the norm. Looking at the cancer risk in UC patients from this perspective, it therefore seems unreasonable to exclude these patients from a Barrett's cancer surveillance program.

Conflict of interest The authors declare that they have no conflicts of interest.

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