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Clinical characteristics may distinguish patients with esophageal adenocarcinoma arising from long- versus short-segment Barrett's esophagus

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ABSTRACT

Background and aims: Patients with long-segment Barrett's esophagus (LSBE; ≧3 cm) have higher risk of developing esophageal adenocarcinoma (EAC) than those with short-segment Barrett's esophagus (SSBE; <3 cm). However, it is unclear whether patients developing EAC from LSBE or SSBE differ significantly according to baseline clinical characteristics.

Methods: We conducted a retrospective analysis of a prospectively maintained database comprising consecutive patients with early EAC treated by endoscopic mucosal resection at a single, tertiary-referral center. Information regarding baseline clinical characteristics were determined. Univariate and multivariate logistic regression were performed to identify factors that differed significantly between patients with EAC arising from SSBE and LSBE.

Results: A total of 145 LSBE EAC and 179 SSBE EAC cases were identified. The LSBE EAC patients had a stronger association with having a hiatal hernia compared to the SSBE EAC patients. In contrast, inverse associations were observed in LSBE EAC patients with statin use and smoking pack-years relative to SSBE EAC patients.

Conclusions: Patients who developed EAC on a background of LSBE were more likely to have a hiatus hernia compared to patients with SSBE EAC, who were more likely to have higher smoking pack-years and higher rates of statin use.

1. Introduction

Barrett's esophagus (BE) is the major risk factor for esophageal adenocarcinoma (EAC) [1], which has a dismal prognosis with a 5-year survival rate of <19% [2]. Although several studies have determined predictors of progression from BE to EAC, there remain many unanswered questions. A longer segment of BE has often been identified as an important risk factor for the development of EAC [3–6], with one study demonstrating that annual risk for adenocarcinoma transition from BE is increased 7-fold with long-segment BE (LSBE) compared to with short-segment BE (SSBE) (0.22% and 0.03%, respectively) [6]. While LSBE was generally thought to gradually elongate from SSBE, several papers have suggested that BE length does not significantly change over time but is established at the time of the initial endoscopy [7–9]. If this hypothesis is true, patients with SSBE and LSBE may have different clinical or genetic characteristics that could potentially determine the BE length. In fact, previous reports indicated that there were significant epigenetic differences between SSBE and LSBE thought to be the result of dietary and other lifestyle factors, which may play an important role in Barrett's carcinogenesis [10,11]. However, there are few studies that have examined patient characteristics between patients with SSBE and LSBE [12–14]. Furthermore, to our knowledge, a comparison of characteristics among patients with EAC arising from SSBE and LSBE has only been previously evaluated by a single, small cohort study [15]. Therefore, it remains unclear if patients developing EAC from LSBE vs. SSBE differ significantly in terms of their baseline clinical characteristics. Clarifying this uncertainty may help to elucidate the relationship between patient factors and Barrett's carcinogenesis in its progression to EAC. Hence, we conducted a retrospective analysis of a prospectively maintained database of patients with EAC to identify factors that are strongly associated with the development of EAC arising from LSBE and SSBE by com-

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paring clinical characteristics that differ between patients in each group.

2. Patients and methods

2.1. Patients

A retrospective analysis was performed of a prospective database comprised of consecutive patients who underwent endoscopic mucosal resection (EMR) for early esophageal adenocarcinoma (T1a and T1b) in Barrett's esophagus with or without subsequent radiofrequency ablation (RFA) or other ablative techniques at a single, tertiary-referral center in Toronto, Canada from May 2001 through October 2016. The study was carried out in accordance with the Declaration of Helsinki and was approved by the St. Michael's Hospital research ethics committee on December 19, 2008. We excluded patients who did not undergo EMR because of the absence of precise histopathological staging in those cases. We also excluded patients with T2 or deeper adenocarcinoma. The final T-staging diagnosis was based on pathology from the EMR specimen. All patients provided informed consent for their participation in our database, and provided detailed information via a demographic, medical history and lifestyle questionnaire that ascertained characteristics such as age, sex, ethnicity, height, weight (BMI: body mass index), current illnesses, family history of malignancy, smoking and alcohol history. GERD-related symptoms (defined as having at least two episodes of reflux symptoms within the most recent three months) and medications including proton pump inhibitors (PPIs), low-dose aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs) and statins (because these medications have been shown to potentially reduce the risk of EAC among patients with BE [16,17]).

2.2. Endoscopy

To determine BE length, we used the top of the gastric folds as the landmark denoting the gastroesophageal junction. Based on the Prague criteria [18], we noted the circumferential (C) and maximum (M) length of BE, and classified BE into long- and short-segment accordingly, depending on whether or not the circumferential extent of BE was longer than 3 cm (SSBE; C < 3 cm, LSBE; C ≥ 3 cm, respectively) [19]. Patients who underwent their index endoscopy prior to the establishment of the Prague criteria were classified by calculating C and M from the description of the BE as reported by the endoscopist. The recorded distance from the diaphragm to the gastroesophageal junction was used to determine the presence or absence of a hiatus hernia. Multiple, 4-quadrant biopsies were obtained every 1–2 cm based on the Seattle protocol to identify intestinal metaplasia or dysplasia. EMR was performed when we found a visible lesion or to completely eradicate BE via radical EMR, particularly for SSBE.

2.3. Pathology

Biopsy and EMR specimens were fixed in 10% neutral buffered formalin, embedded in paraffin and stained with hematoxylin and eosin staining. All specimens were analyzed by at least two experienced gastrointestinal pathologists. A diagnosis of BE was made based on the presence of intestinal metaplasia with goblet cells. Pathological reports were recorded in accordance with the Vienne classification [20] and EMR reports included the information such as grade of differentiation (G), depth of invasion according to the Vieth & Stolte system (m1-4, sm1-3) [21], vertical and horizontal margin and the presence or absence of lympho-vascular invasion (LVI).

2.4. Statistical analysis

All data were expressed as the mean ± standard deviation. Differences between groups were analyzed using the Chi-square test and Fisher's exact test for categorical data, the Student *t*-test for comparing means and the Mann-Whitney *U* test for comparing medians for continuous data. Logistic regression was performed to assess for differences in clinical and pathologic characteristics between the LSBE and SSBE groups. The factors that had important differences in univariate analysis (defined as $P < 0.1$) were included in the multivariate logistic regression analysis. We calculated odds ratios (OR) and 95% confidence intervals (CI) by multivariate logistic regression analysis using StatFlex software (Artech Co., Osaka, Japan). Two-sided *P*-values < 0.05 were considered statistically significant.

3. Results

3.1. Clinical characteristics

We identified 324 patients who underwent EMR for T1a and T1b esophageal adenocarcinoma arising from BE during the study period. Patient clinical characteristics are summarized in Table 1. Of these, 145 patients (45%) had EAC arising from LSBE (mean age 66 ± 11.9 years; 122 men (84%)) and 179 patients (55%) had EAC arising from SSBE (mean age 67 ± 10.8 years; 152 men (85%)). In both groups, male (overall 85%) and white (overall 92%) patients were predominant. There were no significant differences between the groups with regards to a history of diabetes, hypertension or family history of malignancy, with a non-significant trend toward lower BMI in the LSBE compared to the SSBE groups (28.2 ± 5.7 vs 29.5 ± 6.4, $P = 0.07$). In contrast, the LSBE group was significantly more likely to have ongoing GERD symptoms compared to patients in the SSBE group (46% vs. 33%, $P = 0.02$). With respect to smoking status, patients with LSBE were less likely to have ever been smokers compared to the SSBE patients (69% vs 80%, $P = 0.03$), and among those who were smokers, the magnitude of smoking consumption measured in pack-years was also significantly lower for the LSBE group than for the SSBE group (19.6 ± 23.0 vs 25.8 ± 26.7, $P = 0.03$) for the patients in whom this data were available (n = 307). In contrast, no significant differences with regard to alcohol consumption were observed between the two groups. With respect to medication use, we found that the LSBE group were less likely to have used statins compared to the patients in the SSBE group (40% vs 53%, $P = 0.03$), while there were no significant differences regarding use of PPIs, low-dose aspirin and NSAIDs.

With regard to endoscopic findings, the mean circumferential extent of BE (Prague C) in the LSBE and SSBE groups were 6.5 ± 3.4 cm and 0.4 ± 0.6 cm, respectively ($P < 0.001$) and the mean maximal extent of BE (Prague M) was 7.9 ± 3.4cm and 2.7 ± 1.8 cm, respectively ($P < 0.001$). A hiatus hernia was seen more frequently in the LSBE group compared to the SSBE group (84% vs 73%, $P = 0.02$).

3.2. Logistic regression analysis

Univariate logistic regression identified the following variables as being potentially significant differences between the LSBE and the SSBE groups: BMI, smoking pack-years, GERD symptoms, use of statins and the presence of a hiatus hernia. We found that smoking pack-years, statins and hiatus hernia had significant differences that persisted in the multivariate analysis as shown in Table 2. Patients with increasing pack-years of smoking and those who were taking statins were more likely to have developed EAC from SSBE rather than from LSBE, whereas patients with a hiatus hernia had an

Table 1
Patient characteristics.

	LSBE EAC (n = 145)	SSBE EAC (n = 179)	*P* value
Age, years (mean ± SD)	66.4 ± 11.9	66.9 ± 10.8	0.70
Sex (male)	122/145 (84.1%)	152/179 (84.9%)	0.85
Race (white)	134/138 (97.1%)	165/168 (98.2%)	0.71
BMI (mean ± SD)	28.2 ± 5.7	29.5 ± 6.4	0.07
Diabetes	32/139 (23.0%)	45/171 (26.3%)	0.50
Hypertension	69/135 (51.1%)	92/167 (55.1%)	0.49
Family history of malignancy	80/136 (58.8%)	103/166 (62.0%)	0.57
GERD symptoms	63/137 (46.0%)	56/169 (33.1%)	**0.02**
Smoking			
Ever smoking	97/141 (68.8%)	137/172 (79.7%)	**0.03**
Current smoking	15/141 (10.6%)	26/171 (15.2%)	0.24
Pack-years (mean ± SD)	19.6 ± 23.0 (n = 139)	25.8 ± 26.7 (n = 168)	**0.03**
Alcohol			
Ever alcohol	87/139 (62.6%)	109/169 (64.5%)	0.73
Current alcohol	56/132 (42.4%)	78/165 (47.3%)	0.40
Medication use			
PPIs	111/130 (85.4%)	141/163 (86.5%)	0.78
Low-dose aspirin	41/138 (29.7%)	59/170 (34.7%)	0.48
NSAIDs	15/138 (10.9%)	12/166 (7.2%)	0.27
Statins	56/139 (40.3%)	89/169 (52.7%)	**0.03**
Endoscopy			
Prague C (mean), cm	6.53 ± 3.35	0.35 ± 0.64	**<0.001**
Prague M (mean), cm	7.89 ± 3.41	2.67 ± 1.77	**<0.001**
Hiatus hernia	121/145 (83.4%)	130/179 (72.6%)	**0.02**

EAC, Esophageal adenocarcinoma; LSBE, long-segment Barrett's esophagus; SSBE, short-segment Barrett's esophagus; BMI, body mass index; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor; NSAID, non-steroidal anti-inflammatory drug.

Table 2
Odds ratios of having LSBE EAC vs. SSBE EAC.

	Odds ratio	95% Confidence interval	*P* value
BMI	0.89 (per 5.0 increase)	0.73–1.09	0.25
Smoking pack-years	0.89 (per 10.0 increase)	0.81–0.98	**0.02**
GERD symptoms	1.62	0.997–2.65	0.05
Taking statins	0.61	0.38–0.99	**0.04**
Presence of hiatus hernia	1.87	1.02–3.45	**0.04**

LSBE, Long-segment Barrett's esophagus; SSBE, short-segment Barrett's esophagus; EAC, esophageal adenocarcinoma; BMI, body mass index; GERD, gastroesophageal reflux disease.

increased likelihood of having EAC develop from LSBE rather than from SSBE.

3.3. Pathological features

A comparison of the pathological features and clinical follow-up status between patients in the LSBE and SSBE groups is summarized in Table 3. There were no significant differences between the groups in terms of depth of tumor invasion, tumor differentiation, lympho-vascular invasion and rate of positive vertical (deep) margin.

Table 3
Pathological features of EAC.

	LSBE EAC (n = 145)	SSBE EAC (n = 179)	*P* value
Pathological features			
EAC depth			
M1	32 (22.1%)	33 (18.4%)	
M2	32 (22.1%)	43 (24.0%)	
M3	23 (15.7%)	30 (16.8%)	
M4	45 (31.0%)	52 (29.1%)	
SM1	10 (6.5%)	14 (7.8%)	
Deeper than SM2	3 (2.1%)	7 (3.9%)	0.88
Differentiation			
G1	93 (64.1%)	119 (66.5%)	
G2	42 (29.0%)	53 (29.6%)	
G3	10 (6.9%)	7 (3.9%)	0.49
Lympho-vascular invasion	16 (11.0%)	13 (7.3%)	0.24
Vertical margin positive rate	13 (9.0%)	19 (10.6%)	0.62

EAC, Esophageal adenocarcinoma; LSBE, long-segment Barrett's esophagus; SSBE, short-segment Barrett's esophagus.

4. Discussion

This is the first study to compare clinical characteristics of patients with EAC arising from SSBE and from LSBE using a large prospective cohort. Our study suggests that patients who develop EAC from LSBE and SSBE differ based on their baseline clinical characteristics.

LSBE was formerly thought to be the result of SSBE elongation due to repeated inflammation caused by reflux of gastric and bile juice. However, some recent studies have not corroborated this theory. Moawad et al. revealed that BE length does not significantly change over time and observed no significant difference in BE length regardless of patient age at initial endoscopy in a large cohort study [9]. This suggests that BE length is not determined simply by advancing age or cumulative exposure to reflux, but that there may be other factors that determine an individual's response to reflux injury. Dickman et al. demonstrated that patients with a hiatal hernia or using H2 receptor antagonists were more likely to have LSBE whereas patients who were smokers or using PPI were more likely to have SSBE [13], thus illustrating a correlation between clinical characteristics and individual BE length. Furthermore, Jin et al showed that *CDH13* and *MAL* hypermethylation, which have been identified as a common molecular event contributing to carcinogenesis in several cancers, has a strong correlation with BE length and risk of progression to EAC [10,11]. Since several kinds of hypermethylation are thought to be associated with lifestyle habits and metabolic diseases, such as smoking and hyperlipidemia [22,23], these epigenetic alterations, which may be brought on by lifestyle behaviors, may play an important role in the varying development of EAC between SSBE and LSBE patients.

Cigarette smoking is a well-known risk factor for the development of both BE and EAC [24,25]. Smoking reduces lower

esophageal sphincter pressure and increases reflux events, most likely due to nicotine [26]. In addition, smoking is associated with increased DNA damage in BE mucosa, which may contribute to developing EAC [27]. However, the precise role of smoking in EAC carcinogenesis remains unclear. Our present study found that patients with higher pack-years of smoking are more likely to have EAC that arises from SSBE rather than from LSBE. This is consistent with the findings of another study that showed that active smokers are more likely to have SSBE rather than LSBE [14]. Similarly, Nobukawa et al. found that patients with HGD or early EAC arising from SSBE were more likely to be smokers than were patients with HGD or early EAC arising from LSBE in a small cohort study (n = 47) [15]. Our study is the first to demonstrate the relationship between cigarette smoking, smoking pack-years and the length of BE with EAC using a large prospective cohort. Our study, as well as previous reports, indicates that cigarette smoking seems to play a more significant role in the carcinogenesis of EAC arising from SSBE rather than from LSBE.

Whereas patients with LSBE have traditionally been thought to be at increased risk for EAC, in our cohort an even greater number of EAC cases were observed to arise from SSBE. Cigarette smoking appears to be significantly associated with an increased risk of cancer in SSBE and may possibly act to accelerate carcinogenesis. We postulate that cigarette smoking may heighten carcinogenesis risk such that SSBE patients who are smokers may have malignant risks that approach those seen in patients with long-segment disease. Further investigation, including with basic research, is needed to clarify these relationships.

Our present study revealed that the patients with EAC arising from LSBE were less likely to use of statins compared to the patients with SSBE EAC. There might be the possibility that hyperlipidemic patients who need to take statins have higher chance to have EAC arising from SSBE rather than LSBE. Metabolic syndrome including hyperlipidemia has a close relationship with obesity which contributes not only to increasing acid reflux due to mechanical disruption of the gastroesophageal junction, but also promotes a proinflammatory state by releasing adipocytokines [28]. This relationship could be one of the explanations of EAC arising from SSBE; however, the relationship between statins and EAC arising from LSBE is still unclear. Although the interpretation of current statin finding is difficult, we cannot ignore this novel result. Further basic approaches are needed to clarify these questions.

PPIs, aspirin and NSAIDs are well known drugs to have potential protective roles against EAC development [29,30]; however, there were no significant differences in the proportions of these drug administrations between SSBE and LSBE EAC groups in our study. Although we have no doubt that these drugs play important roles on EAC development, they may not affect the differentiation into SSBE or LSBE. As this study result was from a single center experience, it is too early to draw any conclusion.

There are several limitations to our current study. First, because of the retrospective nature of the analysis, the identified associations do not imply causation. Furthermore, the analysis is limited to the variables that were recorded in our prospective database and may miss other important, deterministic variables such as visceral obesity that were never measured. Second, we excluded T2 or more advanced tumor cases. Although this can be the major limitation of this study, the tumor with advanced stage occasionally makes it difficult to determine whether the origin of tumor is from stomach or esophagus. Therefore, we included only cases with early stage EAC to recruit only the true Barrett's cases.

In contrast, a major strength to our study is the large number of EAC cases included. In fact, this is the first study to compare patient characteristics between EAC arising from SSBE vs. LSBE using a prospective cohort of this size. Another strength is that our data includes exposure-response relationships between pack-years of smoking rather than just the presence or absence of a smoking history. Lastly, all pathological EAC diagnoses were based upon EMR resection specimens and not simply from mucosal biopsies. Distinguishing HGD from EAC can be difficult on biopsy specimens and there are often discordant results between the referral biopsy and EMR specimen pathology. By only including confirmed cases of EAC based on EMR specimens, we reduced patient heterogeneity by focusing only on EAC and not a mixed population that also included HGD.

In conclusion, we have identified differences in baseline clinical characteristic between patients with EAC arising from LSBE and SSBE. Patients who developed EAC on a background of LSBE were more likely to have a hiatus hernia and less likely to use statin medications, compared to patients with SSBE EAC, who were associated with increased pack-years of smoking consumption. Although the causal significance of our findings remains unclear, they may identify areas for further research in the mechanisms of Barrett's carcinogenesis, and the differential development of EAC in patients with SSBE and LSBE. Finally, while patients with SSBE traditionally have been considered to be at reduced risk for EAC, those with a significant history of cigarette smoking pack-years may need closer monitoring than suggested by current guidelines, if it becomes clear that they are truly at increased risk for EAC.

Conflict of interest

None declared.

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