Predictive Factors of Barrett Esophagus

Multivariate Analysis of 502 Patients With Gastroesophageal Reflux Disease

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Hypothesis: Risk factors for the presence and extent of Barrett esophagus (BE) can be identified in patients with gastroesophageal reflux disease (GERD).

Design: Case-comparison study.

Setting: University tertiary referral center.

Patients: Five hundred two consecutive patients with GERD documented by 24-hour esophageal pH monitoring and with complete demographic, endoscopic, and physiological evaluation, divided in groups according to the presence and extent of BE (328 patients without BE and 174 with BE [67 short-segment BE and 107 long-segment BE]).

Main Outcome Measures: Clinical, endoscopic, and physiological data, studied by multivariate analysis, to identify the independent predictors of the presence and extent of BE.

Results: Seven factors were identified as predictors of BE. They were abnormal bile reflux (odds ratio [OR], 4.2; 95% confidence interval [CI], 1.9-9.7), hiatal hernia larger than 4 cm (OR, 4.1; 95% CI, 2.1-8.0), a defective lower esophageal sphincter (OR, 2.7; 95% CI, 1.4-5.4), male sex (OR, 2.6; 95% CI, 1.6-4.3), defective distal esophageal contraction (OR, 2.2; 95% CI, 1.4-3.5), abnormal number of reflux episodes lasting longer than 5 minutes (OR, 2.2; 95% CI, 1.1-4.6), and GERD symptoms lasting for more than 5 years (OR, 2.1; 95% CI, 1.4-3.2). Only abnormal bile reflux (OR, 4.8; 95% CI, 1.7-13.2) was identified as a predictor of short-segment BE (baseline, no BE). Three factors were identified as predictors of long-segment BE (baseline short-segment BE). They were hiatal hernia larger than 4 cm (OR, 17.8; 95% CI, 4.1-76.6), a defective lower esophageal sphincter (OR, 16.9; 95% CI, 1.6-181.4), and an abnormal longest reflux episode (OR, 8.1; 95% CI, 2.8-24.0).

Conclusions: Among patients with GERD, specific factors are associated with the presence and extent of BE. Elimination of reflux with an antireflux operation in patients with 1 or more of these factors may prevent the future development of BE.

Barrett Esophagus (BE), the acquired transformation of normal esophageal squamous epithelium into specialized columnar epithelium with goblet cells, is a complication of increased reflux of gastric juice into the distal esophagus.1-3 The factors that lead to the development of BE in some patients with gastroesophageal reflux disease (GERD) and the reasons why short-segment BE (SSBE) develops in some and long-segment BE (LSBE) in others remain incompletely understood.4,5 Further, it is unknown whether SSBE merely represents an earlier stage of LSBE, or if SSBE and LSBE occur as a consequence of different processes.

The clinical importance of both SSBE and LSBE lies in the fact that each is associated with an increased risk of malignancy compared with patients without BE.6 Consequently, surveillance endoscopy has been recommended for all patients with BE7,8 and has been demonstrated to result in the detection of esophageal adenocarcinoma at an earlier, more curable stage.9 The problem has been that most patients with reflux-related adenocarcinoma of the esophagus never had a precancer diagnosis of BE, and consequently, they were not in a surveillance program.10,11 Ideally, individuals with GERD and at increased risk for development of BE would be identified prospectively. Such patients could then undergo definitive antireflux surgery with the intent of preventing the development of BE or, alternatively, be followed more closely. Therefore, the identification of pathophysiological factors predictive of the presence and extent of BE is a clinically important goal. The aim of this study was to identify, by means of a multivariate analysis, factors predictive of the presence and extent of BE.
PATIENTS AND METHODS

STUDY POPULATION

The study population consisted of 502 patients with GERD documented by abnormal acid exposure on 24-hour esophageal pH monitoring (composite acid score >14.76) (343 men and 159 women; median age, 52 years [age range, 15-86 years]). All patients were evaluated in the Department of Surgery, Keck School of Medicine, University of Southern California, Los Angeles, between August 1991 and February 1999. In addition to 24-hour pH testing, all patients completed a standard questionnaire, underwent upper gastrointestinal tract endoscopy with extensive protocol-based biopsies, and had lower esophageal sphincter (LES) and esophageal body manometry. The presence of Helicobacter pylori infection was evaluated in 382 patients by gastric biopsy. Two hundred six patients were evaluated for the reflux of bilirubin into the esophagus using a Bilitec probe (Medtronic Functional Diagnostics, Shoreview, Minn). Patients with named motility disorders and those with a history of previous esophageal or gastric surgery were excluded from the study.

DATA COLLECTION AND DEFINITIONS

A standard questionnaire was used to discern the presence and duration of typical reflux symptoms (heartburn, regurgitation, and dysphagia) as well as atypical or extraesophageal symptoms, such as chest or epigastric pain, aspiration symptoms, recurrent pneumonia, wheezing, or persistent cough. Body mass index (BMI) was calculated for each patient using the following formula:

\[
\text{BMI} = \frac{\text{weight in pounds} \times 703}{\text{height in inches}^2}
\]

Patients were classified as normal (BMI, 19-25), moderately obese (BMI, 25.1-35), and morbidly obese (BMI, >35).

Lower esophageal sphincter pressure was measured by a stationary pull-through technique as the mean pressure of 5 recordings at the respiratory inversion point. The overall and abdominal lengths of the LES were calculated from the mean of 5 recordings as previously described. A structurally defective sphincter was defined by a resting pressure of less than 6 mm Hg, an overall length less than 2 cm, or an abdominal length less than 1 cm. Esophageal body motility was assessed using a 3-hole catheter and a water perfusion technique as previously described. We analyzed a total of 10 wet swallows (5 mL of distilled water), with a 20-second interval between each. Defective esophageal body motility was defined by the presence of distal esophageal contraction amplitudes below the fifth percentile of normal (36 mm Hg). The limit of normal for each parameter measured during the 24-hour pH monitoring period was defined as the 95th percentile from a group of healthy volunteers. The pattern of esophageal acid exposure was determined based on the 24-hour pH test as previously described. Postprandial reflux was defined as abnormal percent time with esophageal pH less than 4 during the 2-hour postprandial period (>8.4%) in the setting of normal upright and supine acid exposure; upright reflux, abnormal percent time with esophageal pH less than 4 only in the upright position (>8.4%) and regardless of whether the postprandial exposure was normal or abnormal; supine reflux, abnormal percent time with an esophageal pH less than 4 only in the supine position (>3.4%); and bipositional reflux, abnormal percent time with an esophageal pH less than 4 in both the upright and supine positions.

Esophageal bilirubin monitoring (Bilitec 2000; Medtronic Synectics, Shoreview, Minn) was performed simultaneously with pH monitoring in a subset of 206 patients. An absorbance threshold of 0.2 was selected, and bilirubin exposure was considered abnormal when greater than 1.7% of the total time was above this threshold as previously described.

Upper gastrointestinal endoscopy was performed in all patients. The location of the gastroesophageal junction (GEJ) was defined as the site where the proximal extent of the gastric rugal folds met the tubular esophagus. A hiatal hernia was diagnosed when the difference between the position of the crural impression, identified by having the patient sniff, and the gastroesophageal junction was 2 cm or more. The size of the hiatal hernia was noted. A columnar-lined esophagus (CLE) was suspected when the squamocolumnar junction or any part of its circumference extended above the GEJ. This included an irregular squamocolumnar junction with tongues of columnar mucosa extending into the esophagus. The presence of a CLE was confirmed by histological evaluation of biopsy specimens. When a columnar-lined segment was observed, multiple biopsy specimens were obtained from the area, and

RESULTS

UNIVARIATE ANALYSIS

Three hundred twenty-eight patients with GERD but no BE were compared with 174 patients with GERD and BE (67 SSBE and 107 LSBE). Table 1 presents the age, sex, body mass index, and duration of GERD symptoms in patients without BE and in those with SSBE and LSBE. The proportion of male patients and the duration of GERD symptoms was lowest in patients without BE and highest in patients with LSBE. There was no significant difference in age, BMI, and H pylori infection status between groups.

As presented in Table 2, the prevalence of hiatal hernia was higher, and the hernias were larger in patients with LSBE than in patients with SSBE; and larger in patients with SSBE compared with those without BE. Likewise, the manometric characteristics of the LES were most abnormal in patients with LSBE. In patients with SSBE, the LES pressure was significantly lower than it was in patients without BE. Distal esophageal body motility was similar in patients with SSBE and LSBE, but both were significantly worse compared with that of patients without BE.

As presented in Table 3, all parameters from the 24-hour esophageal pH monitoring became progressively more abnormal going from patients without BE to
at each level the distance from the incisors was recorded. Biopsy specimens were fixed in 10% buffered formalin, em- bedded in paraffin, sectioned, mounted on slides, and stained with hematoxylin-eosin using standard techniques. Intesti- nal metaplasia was defined by the presence of a columnar epithe- lum with a villiform surface, mucous glands, and well- defined goblet cells. The presence of goblet cells was confirmed by positive staining with Alcian blue at pH 2.5. Barrett esopha- gus was identified by the presence of an endoscopically visible segment of columnar lining in the distal esophagus, regard- less of length, with histological analysis demonstrating goblet cell indicative of intestinal metaplasia. Short- segment BE vs LSBE was determined in each patient based on the length of columnar epithelium (<3 cm or ≥3 cm, respectively). Biopsy specimens from the gastric antrum were evaluated in a subset of 382 patients for the presence of H pylori infection using a Giemsa stain.

DEFINITION OF STUDY VARIABLES

Dependent/Outcome Variables

The outcome of interest in this analysis was the presence and extent of BE. Consequently, 3 comparison groups were used: patients without BE, patients with SSBE, and patients with LSBE.

Independent/Potentially Predictive Variables

The numerical independent variables studied at the univariate level were as follows: age; BMI; duration of GERD symptoms; size of hiatal hernia; percent total time with esophageal acid exposure less than 4; number of reflux episodes, number of reflux episodes lasting longer than 5 minutes, and the duration of the longest reflux episode on 24-hour esophageal pH monitoring; percent time of Bilitec probe absorp- tion greater than 0.2 on 24-hour esophageal bilirubin moni- toring; LES length and pressure; and distal esophageal contraction amplitudes. The categorical variables studied at the univariate level were as follows: sex; pattern of esoph- ageal acid exposure; and the presence of a hiatal hernia, defective LES, defective distal esophageal contraction amplitudes, and abnormal bilirubin exposure.

To simplify clinical interpretation and for optimal use of the logistic regression method, the potentially predic- tive variables were converted to categorical data. The vari- ables regarding hiatal hernia and numerical variables from the 24-hour esophageal pH monitoring were divided into 3 categories (normal, abnormal to the calculated 75th per- centile of the study population; abnormal, above the calculated 75th percentile of the study population). This permitted us to study the association between BE and the presence and size of a hiatal hernia, as well as individual parameters from the 24-hour pH monitoring test. The vari- ables were (1) age (<50 years and ≥50 years); (2) sex (male or female); (3) BMI (normal, 19-25; obese, 25-35; or morbidly obese, >35); (4) duration of GERD symptoms (<5 years and ≥5 years); (5) hiatal hernia (no hiatal hernia, hia- tal hernia 2-4 cm, hiatal hernia >4 cm); (6) percent total time esophageal pH less than 4 (normal: 0 to 4.4%; 4.5 to 14.7% and >14.7%); (7) number of reflux episodes (normal: <47, 47-167 and >167); (8) number of reflux epi- sodes >5 min (normal: 0-3; 4-7 and >7); (9) longest re- flux episode (normal: 0-19.8, 19.9-31.7 and >31.7); (10) pattern of esophageal acid exposure (posprandial, upright, supine, or bipositional); (11) bilirubin exposure (normal: 0-1.7% and abnormal >1.7%); (12) H pylori infection status (no infection or infection); (13) LES competence (competent or defective); and (14) distal esophageal amplitude (normal, ≥36; or hypocontractive, <36 mm Hg).

STATISTICS

Values are expressed as medians and interquartile ranges unless otherwise stated. A univariate analysis was performed to assess the isolated effect of each variable on the presence and extent of BE. Continuous variables were studied using their numerical values and previously defined categorical variables. The χ² test was used to compare propor- tions between groups, and the Mann-Whitney U test was used to compare distribution of continuous variables be- tween individual groups. Statistical significance was con- sidered to be α ≤.05.

Forward stepwise logistic regression was performed to assess the joint effect of all potentially predictive vari- ables and to define those that are independently associ- ated with the presence and extent of BE. To stay in the model, variables were required to be significant at α ≤.05. The variables found to be significant were then analyzed in a multivariate model to obtain the predictive effect of each adjusted for the presence of the other significant vari- ables (adjusted odds ratio [OR]). The software SPSS 10.0.1 (Statistical Product and Service Solutions 10.0.1 Standard Version for Windows; SPSS Inc, Chicago, Ill) was used for all statistical analyses.

those with SSBE and LSBE. The prevalence of biposi- tional reflux also increased progressively from patients without BE to those with SSBE and LSBE. Lastly, while bile exposure in the distal esophagus was similar in pa- tients with SSBE and LSBE, it was significantly higher in both groups compared with patients without BE.

MULTIVARIATE ANALYSIS

All variables identified as independently predictive for the presence of BE by multivariate analysis are listed in rank order in Table 4. The strongest predictor was the pres- ence of bile in the distal esophagus, as indicated by in- creased esophageal bilirubin exposure. Abnormal bile re-

COMMENT

Multivariate analysis identified 7 factors predictive of the presence of BE in patients with GERD. They were in- creased esophageal bile exposure, alteration of the geometry of the gastroesophageal junction by a hiatal hernia, loss of the gastroesophageal barrier manifested
by a defective LES, male sex, duration of reflux symptoms, and poor esophageal clearance manifested by defective distal esophageal contraction amplitudes and an increased number of reflux episodes lasting longer than 5 minutes.

Of the 7 factors, increased esophageal bile exposure was the strongest predictor of the presence of BE. This finding confirms previous clinical and experimental studies that emphasized the importance of duodeno-gastroesophageal reflux in the pathogenesis of BE.21-24 In 1984, using 24-hour esophageal pH monitoring to measure, the first suggestion of increased esophageal exposure to alkaline juice in patients with BE was reported.25 This was subsequently shown to be bile by aspiration studies26 and Bilitec monitoring.20 Using both a pH and a Bilitec probe, it was shown that increased esophageal bilirubin exposure could occur in conjunction with increased acid exposure.27 Subsequently, the toxic and synergistic action of refluxed duodenal and gastric contents into the esophagus and its greater occurrence in patients with BE has been repeatedly shown in the literature.17,27-30 The results of the current study further confirm the important association between increased esophageal bilirubin exposure and the presence of BE.

The second and third most important predictors of BE were a hiatal hernia larger than 4 cm and a defective LES. Both of these factors are associated with the function of the gastroesophageal reflux barrier. In a recent study, it was shown by univariate analysis that 96% of patients with BE had a hiatal hernia, compared with 42% of the control group ($P < .001$).31 In the 1950s, Marchand32 used cadavers to eloquently demonstrate that the loss of the normal angle of His that occurs in association with a hiatal hernia distorts the geometry of the gastroesophageal junction and impairs function of the LES. In live subjects, Ismail et al33 confirmed these findings by comparing the yield pressure at which the cardia opened in response to gastric distension in subjects of varying size with hiatal hernias. There is increasing evidence that the size of a hiatal hernia correlates with the severity of reflux disease, which is likely a consequence of progressive esophageal mucosal injury with esophageal body scarring and shortening.16,34-36

In addition to a large hiatal hernia, a defective LES is also associated with BE, occurring in 93.8% of the patients without BE, 82.2% of those with short-segment BE, and 99.1% of those with long-segment BE. The data also showed that the prevalence of hiatal hernia, prevalence of defective LES, LES total length, LES abdominal length, and LES pressure were all significantly higher in patients with BE compared to those without BE. The prevalence of abnormal distal esophageal amplitude and distal esophageal amplitude were also significantly higher in patients with BE.

### Table 1. Demographic Data and Helicobacter pylori Infection in Patients Without BE, and Those With SSBE and LSBE

<table>
<thead>
<tr>
<th>Variable</th>
<th>No BE (n = 328)</th>
<th>SSBE (n = 67)</th>
<th>LSBE (n = 107)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), y</td>
<td>52 (15-86)</td>
<td>53 (20-86)</td>
<td>51 (22-83)</td>
<td>. . .</td>
</tr>
<tr>
<td>% Male</td>
<td>62.8</td>
<td>73.1</td>
<td>82.2</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Male-female ratio</td>
<td>1.7:1</td>
<td>2.7:1</td>
<td>4.6:1</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Median body mass index (range)</td>
<td>26.9 (15.0-48.7)</td>
<td>27.6 (19.8-37.9)</td>
<td>27.0 (20.6-44.9)</td>
<td>. . .</td>
</tr>
<tr>
<td>Median duration of symptoms, y</td>
<td>10</td>
<td>12</td>
<td>14.1</td>
<td>. . .</td>
</tr>
<tr>
<td>Helicobacter pylori infection, %</td>
<td>13.5</td>
<td>8.9</td>
<td>14.1</td>
<td>. . .</td>
</tr>
</tbody>
</table>

*P value for % male and male/female ratio are by $x^2$ linear trend analysis. All other $P$ values were for individual comparisons between the groups. BE indicates Barrett esophagus; SSBE, short-segment BE; and LSBE, long-segment BE.

### Table 2. Characteristics of the Gastroesophageal Reflux Barrier and Motility of the Distal Esophagus in Patients Without BE and Those With SSBE and LSBE

<table>
<thead>
<tr>
<th>Variable</th>
<th>No BE (n = 328)</th>
<th>SSBE (n = 67)</th>
<th>LSBE (n = 107)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of hiatal hernia, %</td>
<td>55.8</td>
<td>73.1</td>
<td>94.4</td>
<td>$\leq .01^\ddagger$</td>
</tr>
<tr>
<td>Hiatal hernia length, cm</td>
<td>2 (0.3-3)</td>
<td>3 (0.3-3)</td>
<td>4 (3-5)</td>
<td>$\leq .03^\ddagger$</td>
</tr>
<tr>
<td>Prevalence of defective LES, %</td>
<td>69.2</td>
<td>80.6</td>
<td>99.1</td>
<td>$\leq .001^\ddagger$</td>
</tr>
<tr>
<td>LES total length, cm</td>
<td>2.0 (1.4-3.0)</td>
<td>1.8 (1.4-2.8)</td>
<td>1.6 (1.0-2.4)</td>
<td>$\leq .05^\ddagger$</td>
</tr>
<tr>
<td>LES abdominal length, cm</td>
<td>0.8 (0.4-1.4)</td>
<td>0.8 (0.2-1.0)</td>
<td>0.2 (0.0-0.8)</td>
<td>$\leq .01^\ddagger$</td>
</tr>
<tr>
<td>LES pressure, mm Hg</td>
<td>7.0 (4.0-11.6)</td>
<td>5.0 (3.6-8.4)</td>
<td>3.0 (1.6-5.0)</td>
<td>$\leq .01^\ddagger$</td>
</tr>
<tr>
<td>Prevalence of abnormal distal esophageal amplitude, %</td>
<td>20.7</td>
<td>37.3</td>
<td>43.9</td>
<td>$\leq .001$</td>
</tr>
<tr>
<td>Distal esophageal amplitude, mm Hg</td>
<td>64 (42-96)</td>
<td>45 (30-67)</td>
<td>46 (32-61)</td>
<td>$\leq .001$</td>
</tr>
</tbody>
</table>

*Data are given as median (interquartile range) unless otherwise noted. BE indicates Barrett esophagus; SSBE, short-segment BE; LSBE, long-segment BE; and LES, lower esophageal sphincter.

†For all individual comparisons between the groups.
‡For the comparisons no BE vs LSBE and SSBE vs LSBE.
§For the comparison no BE vs SSBE.
¶For the comparison SSBE vs LSBE.
††For the comparison no BE vs SSBE and no BE vs LSBE.
†‡For the comparison SSBE vs LSBE.
patients. Fein et al explored the interplay between the LES and a hiatal hernia and noted that a hiatal hernia places the LES at a mechanical disadvantage, particularly during episodes of gastric distension. When the LES components are defective in the presence of a hiatal hernia, as seen in BE, the effects are additive, and gross incompetency exists. This makes control of reflux difficult with medical therapy. Katzka and Castell as well as Sampliner have shown that in this situation, high-dose proton pump inhibitor therapy is often unsuccessful at normalizing esophageal acid exposure.

Similar to others, we found a higher prevalence of male patients with BE (78%) compared with patients without BE (63%) (P < .001). By multivariate analysis, male sex was determined to be an independent predictor of BE. We noted, as others have, that the male-female ratio approaches 1:1 as the length of BE decreases. In LSBE, where the male-female ratio is 4.6:1, we found that women had the same pathophysiologic derangements as men (data not shown), indicating that fewer women, for reasons unknown, have severe reflux diseases.

The multivariate analysis also identified both decreased distal esophageal contraction amplitudes and an increased number of reflux episodes lasting longer than 5 minutes as independent predictors for the presence of BE. These factors are indicators of impaired esophageal clearance, and they reinforce the importance of prolonged esophageal mucosal contact to refluxed gastric juice in the development of BE. This suggests that the reflux-induced injury extends beyond the mucosa into the muscularis propria of the esophagus and leads to inflammatory damage and scarring of esophageal muscle. Progressive loss of esophageal muscle function can induce a spiral of progressive loss of esophageal clearance, more mucosal injury, and ultimately end-stage esophageal disease.

The duration of GERD symptoms increased significantly across the 3 study groups. In the multivariate analy-
sis, GERD symptoms present for more than 5 years was associated with BE. The length of time necessary to develop BE may provide an opportunity for early surgical intervention to stop reflux and potentially prevent the development of BE. This needs to be the focus of future studies since the ultimate solution for the rising incidence of esophageal adenocarcinoma may be to prevent the development of BE with early surgical therapy in those patients with appropriate risk factors.

It is interesting to note that the percentage of time that the esophagus was exposed to a pH less than 4 on 24-hour monitoring was not a significant independent predictor of the presence of BE. However, an inclusion criteria for this study was the presence of an abnormal score on 24-hour pH monitoring, and by univariate analysis, the percentage of time that the esophageal pH was less than 4 was significantly higher in those with BE. We have previously shown that the length of columnar mucosa without intestinal metaplasia increases progressively with increasing percentage of time that the esophageal pH is less than 4 on 24-hour pH monitoring.47 This gave rise to the theory that columnarization of the distal esophagus is caused by increased esophageal exposure to acid (pH < 4), and that this columnar mucosa is the precursor to BE.5,48 This, while acid exposure is associated with the formation of columnar mucosa, we found that bile exposure had the strongest association with the presence of intestinal metaplasia. Consequently, increased esophageal acid exposure may be a necessary, but not a sufficient factor for the development of BE, since it does not differentiate between those who do and do not develop intestinal metaplasia.

The role of *H pylori* infection in the pathogenesis of GERD and its complications is still controversial. There is evidence suggesting that *H pylori* may protect against the development of erosive esophagitis.46-48 BE, and esophageal adenocarcinoma.48,49 Furthermore, it has been suggested that eradication of *H pylori* may precipitate reflux esophagitis in patients with duodenal ulcers.50-51 In our study population, the prevalence of patients with gastric *H pylori* infection was similar in the study groups and was not related to either the presence or extent of BE.

A second aim of our study was to evaluate the pathophysiologic factors related to the length of BE. Our study showed that BE was associated with an increased esophageal exposure to bilirubin. Interestingly, we also found that the prevalence and degree of increased esophageal bilirubin exposure was not significantly different between patients with SSBE or LSBE. This suggests that abnormal bile reflux is the key determinant associated with intestinal metaplasia, and that other factors determine the length of BE.

By multivariate analysis, 3 independent factors were predictive of the presence of LSBE, whereas the sole predictor for the presence of SSBE was only increased bile exposure. The strongest predictor for LSBE was the presence of a large (> 4 cm) hiatal hernia, followed by a defective LES and long reflux episodes. Taken together, these factors all indicate that patients with LSBE have more profound derangements in their gastroesophageal reflux barrier and consequently more severe reflux disease. While increased bilirubin exposure is the major factor associated with intestinal metaplasia of any length, it is progressive deterioration of the antireflux barrier and the mechanisms of esophageal clearance that seem to be the major factors associated with LSBE.

Importantly, our data show that patients with SSBE have similar pathophysiologic abnormalities as those with LSBE, but to a lesser extent. Thus, SSBE likely represents an earlier stage of disease within the GERD spectrum. Our data refute the theory that BE develops rapidly to its full length without subsequent alteration. This concept is largely based on the longitudinal observation of 21 patients with BE longer than 3 cm published by Cameron and Lomboy.52 Note, however, that all these patients by definition already had LSBE. Our data would suggest that they in all likelihood had large hiatal hernias, a defective LES, and impaired esophageal clearance. Consequently, it is little wonder that they failed to change significantly during the observation period.44,53

We conclude that the independent predictors for the presence of BE are increased esophageal bile exposure, alteration of the geometry of the gastroesophageal junction by a hiatal hernia, a defective LES, male sex, duration of reflux symptoms, and poor esophageal clearance. Of these, increased esophageal exposure to bile is the most important independent predictive factor and was the only independent predictive factor for the presence of SSBE. Identification of these factors in patients without BE and prompt intervention with antireflux surgery may prevent the development of BE. This should become the aim of future prospective surgical studies.

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Silvia Tan, MS, from the Department of Biometry, University of Southern California, was our validating statistician.

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