Prevalence of Barrett’s esophagus in Northern Greece: A Prospective Study (Barrett’s esophagus)

Katsinelos P1,2, Lazaraki G1, Kountouras J3, Chatzimavroudis G1, Zavos C3, Terzoudis S1, Tsiaousi E1,2, Gkagkalis S1,2, Trakatelli C2, Bellou A2, Vasiliadis T1

1Department of Endoscopy and Motility Unit, G. Gennimatas General Hospital, Thessaloniki, Greece
21st Department of Internal Medicine, School of Medicine, Aristotle University of Thessaloniki, Papageorgiou Hospital, Thessaloniki, Greece
32nd Department of Internal Medicine, School of Medicine, Aristotle University of Thessaloniki, Ippokration Hospital, Thessaloniki, Greece

Abstract

Background: Barrett’s esophagus (BE) is a premalignant condition associated with chronic gastro-esophageal reflux disease (GERD). As only a small proportion of BE progresses to malignancy, it is important to study BE prevalence to prevent adenocarcinoma.

Materials and Methods: Between January 2007 and December 2010, all consecutive individuals who underwent routine upper endoscopy were prospectively recruited. Patients referred for GERD were excluded from the study. Clinical and endoscopic data were collected.

Results: A total of 1,990 patients (mean age 47.48±13.4 years; 52.8% males) were included. Of them, 496 (24.9%) reported GERD. Erosive esophagitis (EE) was found in 221 participants (11.1%, 193 patients with LA grade A and 28 patients with LA grade B). Overall 31 of 1494 participants not reporting reflux symptoms (2.07%) suffered from silent GERD. BE was diagnosed in 75 participants (3.77%), four (5.3%) with long-segment BE and 71 (94.7%) with short-segment BE. Low-grade dysplasia was noticed in 1 patient with long-segment BE. Hiatal hernia (HH) was found in 196 patients (9.8%), and mean HH length was 3.22 ± 0.2 cm. BE was correlated to EE, GERD and the presence of HH (p=0.0167, <0.001 and 0.017, respectively) whereas it was not associated with age, alcohol consumption and smoking (p=0.057, 0.099 and 0.06, respectively). BE was not correlated with Helicobacter pylori infection (p=0.542).

Conclusion: The prevalence of BE was 3.77% in a Greek population undergoing upper endoscopy not referred for GERD. Long-segment BE was very uncommon (0.2%) whereas 2.07% of patients not reporting symptoms suffered from silent GERD.

Key words: Barrett’s esophagus, endoscopy, esophago-gastric junction, gastro-esophageal reflux, prevalence

Corresponding Author: Panagiotis Katsinelos, MD, PhD, Assistant Professor of Gastroenterology, Department of Endoscopy and Motility Unit, G. Gennimatas General Hospital, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece, tel/fax: +302310963341, e-mail: gchatzimav@yahoo.gr

Introduction

Barrett’s esophagus (BE) is a premalignant condition associated with chronic gastro-esophageal reflux disease (GERD); GERD is the greatest risk factor associated with BE development1,2. BE is defined as replacement of the normal distal esophageal epithelium by specialized columnar epithelium, characterized by the presence of goblet cells, the key pathologic feature establishing intestinal metaplasia; it is also known as specialized intestinal metaplasia3,4. As proposed in the definition, regardless of which one is considered, the diagnosis with BE requires the identification of intestinal metaplasia (columnar epithelium) by endoscopy and histological confirmation5. BE is considered to follow the sequence intestinal metaplasia - low-grade dysplasia (LG) - high-grade dysplasia (HGD) - adenocarcinoma (AC) development in a subset of patients6. Both short-segment BE (SSBE, <3 cm) and long-segment BE (LSBE, ≥3 cm) may confer a significant risk for the development of AC of the distal esophagus that is increased by the development of dysplasia6. However, as only a small proportion of BE progresses to malignancy7, it is important to study the natural history of silent GERD and BE and to characterize the subgroups, if any, at the greatest risk of progression to malignancy to prevent AC.

Racial differences in the prevalence of BE are controversial; in previous studies, the prevalence of BE in asymptomatic individuals screened by upper endoscopy varied between 1.2-25%8,9,10 and reached 8-20% in patients undergoing endoscopy for GERD11. Furthermore, previ-
ously rare, AC of the esophagus and esophagogastric junction (EGJ) with an annual incidence of 6.0/100,000 persons is now the most common esophageal malignancy in Western countries\textsuperscript{12} whereas previous epidemiologic data displayed mortality from esophageal cancer in Greece among the lowest in the world (3.5 per 100,000 person-years: WHO 1995)\textsuperscript{13}. Regarding BE prevalence in Greece, there is also a paucity of epidemiologic data.

Therefore, the aim of this study was to determine prospectively the prevalence, clinical characteristics, and risk factors of BE, including LSBE and SSBE, in an adult population undergoing upper endoscopy for any indication except reflux disease in a tertiary hospital in Northern Greece.

Materials and methods

Patients

Between January 2007 and December 2010, all consecutive individuals aged between 18 and 75 years who underwent routine upper endoscopy as part of a routine examination in the Department of Endoscopy and Motility of Central Hospital, Thessaloniki, Greece, were prospectively recruited. The majority of these individuals, with or without reflux and/or dyspeptic symptoms, were self-referred for a medical examination to rule out gastrointestinal disorders, particularly malignancy. Other participants were patients referred from their physicians for upper endoscopy in the context of iron-deficiency anemia or to rule out malignancy. Clinical and endoscopic information were collected. All patients had to fill in a questionnaire that included detailed history of reflux symptoms, smoking, and alcohol drinking pattern.

Patients referred for symptoms of GERD were excluded from the study. Additionally, women who were pregnant and individuals who had gastro-esophageal surgery, records of experiencing major psychotic episodes, mental retardation, dementia, or illnesses that might have impaired their ability to complete the questionnaire, certain alarm features (weight loss, odynophagia, dysphagia, bleeding), coagulopathies, thrombocytopenia (<50,000 platelets/mL) and chronic liver disease were also excluded.

The study protocol was approved by the local Ethics Committee of our hospital and all participants gave written informed consent.

Questionnaire and definitions of reflux symptoms and GERD

Prior to endoscopy, clinical information was recorded in a standard structured questionnaire that contained relative questions (items) concerning gastro-esophageal reflux symptoms during the previous 6 months. Other questions included: general condition of the individual (self-reported height and weight); history of illness and operations; personal habits such as smoking (number of cigarettes/day, years of smoking) and alcohol consumption (amount and frequency of alcohol intake per week); use of acid-suppressive drugs, such as H\textsubscript{2}-receptor antagonists and proton pump inhibitors (PPIs), and non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin during the previous 3 months; atypical reflux symptoms (pulmonary, ear, nose and throat symptoms) probably associated with reflux, such as chest pain, globus, chronic cough, laryngitis, asthma\textsuperscript{14}; and other common upper gastrointestinal symptoms such as epigastric pain or discomfort, early satiety, nausea and vomiting.

The interview was conducted by a single experienced investigator (G.L.) who was able to provide participants with a standardized explanation of the questions and definitions of symptomatology. In the present study, heartburn was defined as a burning sensation in the retrosternal area, regurgitation as a bitter- or sour-tasting fluid regurgitating to the throat or mouth\textsuperscript{15}. An individual was defined as having GERD when he/she had experienced troublesome heartburn and/or acid regurgitation during the previous 6 months\textsuperscript{15}. Significant tobacco use was defined as cigarette smoking equal to or exceeding 10 cigarettes/day as previously described\textsuperscript{16}. Alcohol use was defined as the consumption of alcohol (beer, wine, or other beverages containing) of >80 g/d. We calculated body mass index (BMI) based on current height and weight and defined obesity as a BMI ≥ 30 kg/m\textsuperscript{2}\textsuperscript{17}.

Endoscopy and definitions of endoscopic findings

Upper endoscopic examinations were performed using a standard video upper endoscope (Olympus GIF series; Olympus Optical Co., Ltd., Tokyo, Japan). Patients undergoing endoscopy were given topical pharyngeal spray with 10% lidocaine (Xylocaine, Astra-Zeneca, Bedfordshire, UK) followed by intravenous sedation with midazolam (Dormicum, Roche Pharmaceuticals, Nutley, NJ, USA) and fentanyl (Fentanyl, Jansen-Cilag, Neuss, Germany).

Since some participants underwent more than one endoscopy during the study period, the first endoscopy was used as the index endoscopy. One endoscopist (P.K.), with >20 years experience and blinded to the presence of symptoms, independently performed the upper endoscopy, and made the diagnosis according to the Los Angeles (LA) classification of esophagitis\textsuperscript{2}. In addition, photographs taken from the distal esophagus during the endoscopy were reviewed by a second endoscopist. In the event of a discrepancy in the diagnosis, an agreement was reached following discussion between the performing and reviewing endoscopists. During endoscopic examinations, the anatomy of the EGJ region was carefully examined for the squamocolumnar junction (SCJ), recognized by the distinct difference in color between squamous and columnar epithelium, the EGJ itself (defined as the level of the proximal margin of the longitudinal gastric folds), and the diaphragmatic hiatus (identified as the level of impression made by the diaphragmatic crura). The levels of the SCJ, EGJ, and diaphragmatic hiatus were measured during withdrawal of the endoscope at the end of the examination. A diagnosis of hiatus hernia (HH) was made when the gastro-esophageal area stayed open all
the time, squamous epithelium of the distal oesophagus could be seen from the retroflexed endoscopic view and the distance between the muscular ridge of the diaphragm and the EGJ was ≥2 cm. Erosive esophagitis (EE) was defined endoscopically by visible breaks of the distal esophageal mucosa and evaluated for severity according to the LA classification. When a suspected columnar-lined esophagus was identified based on salmon-pink mucosa in either a circumferential upward shift of the SCJ or in adjacent mucosal tongues or islands, biopsies were taken for histologic examination. Biopsies were obtained by using the standard Seattle protocol and four quadrant biopsies were obtained every 2 cm with standard biopsy forceps. The diagnosis of BE was confirmed by the presence of specialized intestinal metaplasia containing Alcian-blue positive goblet cells at a pH of 2.5. Moreover, BE was labeled as SSBE or LSBE based on the length of the columnar-appearing mucosal segment of <3 cm, or ≥3 cm, respectively. Silent GERD was defined when erosive esophagitis and/or BE were present in an individual without reflux symptoms.

**Helicobacter pylori (H. pylori)** infection and co-existing endoscopically identified upper gastrointestinal pathologies were recorded. *H. pylori* status was determined by using a 24-hour rapid urease test (CLOtest, Kimberly-Clark/Ballard Medical Products, Roswell, Utah, USA) on antral biopsy specimens.

### Statistical analysis
We analyzed categorical data by using x² analysis and non-categorical data by using Student’s t test. All statistical calculations were performed by the Statistical Package for Social Science (SPSS, 13.0 Inc., Chicago, Illinois, USA). Statistical significance was set at P<0.05 and all reported P-values were two-sided.

### Results
During the four-year study period, a total of 2603 individuals undergoing routine endoscopy were primarily recruited. Of these, 498 patients who were referred for GERD symptoms, 12 patients who had undergone gastrectomy, 99 with alarm symptoms, 3 patients unable to communicate due to previous cerebrovascular ischemic attack and one with mental retardation, were excluded from the study. Therefore, a total of 1990 patients (mean age 47.48±13.4 years; 52.8% males) were finally included in the study.

A total of 496 people (24.9%) reported GERD symptoms over the previous 6 months. EE was found in 221 participants (11.1%) of whom 17 patients with BE and 14 patients with EE did not report any reflux symptoms during the last six months. Thus, overall 31 of 1,494 participants not reporting reflux symptoms (2.07%) suffered from silent GERD. EE was mild/moderate (193 patients with LA grade A and 28 patients with LA grade B) in all cases. BE was diagnosed in 224 patients during endoscopy (220 patients with SSBE and 4 with LSBE). However, BE was finally diagnosed in only 75 participants (3.77%) that met both endoscopic and histological criteria for BE, four (5.3%) with LSBE and 71 (94.7%) with SSBE, and with a mean age of 52.2±12.1 years. Low-grade dysplasia of BE was noticed in 1 patient with LSBE. In patients with GERD the prevalence of BE was 11.7% and 1.13% for patients without GERD symptoms, respectively. In patients with EE, the prevalence of BE was 9.04%, while in those without EE, it was 3.1%.

HH was found in 196 patients (9.8%), and mean HH length was 3.22 ± 0.2 cm. In patients with and without HH, the prevalence of BE was 8.1% and 3.4%, respectively. Histology samples were found positive for *H. pylori* in 418 of 1990 (21%). The prevalence of *H. pylori* infection did not differ between BE patients and non-BE controls (Table 1).

Clinical and endoscopic characteristics of the patients are shown in Table 1.

### Discussion
In the present series, BE was found in 3.77% (75 of

<table>
<thead>
<tr>
<th>BE group (n=75)</th>
<th>Non-BE group (n=1915)</th>
<th>Total (n=1990)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (m:f)</td>
<td>50:25</td>
<td>1002:913</td>
<td>1052:913</td>
</tr>
<tr>
<td>Age (years) (Mean±SD)</td>
<td>52.2±12.2</td>
<td>47.3±13.2</td>
<td>47.48±13.4</td>
</tr>
<tr>
<td>Body mass index (Mean±SD)</td>
<td>23.7±2.8</td>
<td>23.4±5.1</td>
<td>23.45±5.2</td>
</tr>
<tr>
<td>Smoking</td>
<td>29 (38.7)</td>
<td>552 (28.8)</td>
<td>581 (29.2)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>38 (50.7)</td>
<td>689 (36)</td>
<td>727 (36.53)</td>
</tr>
<tr>
<td>Hiatus hernia</td>
<td>16 (21.3)</td>
<td>180 (9.4)</td>
<td>196 (9.8)</td>
</tr>
<tr>
<td>Erosive esophagitis</td>
<td>20 (26.6)</td>
<td>201 (10.5)</td>
<td>221 (11.1)</td>
</tr>
<tr>
<td>Reflux symptoms</td>
<td>58 (77.33)</td>
<td>438 (22.9)</td>
<td>496 (24.9)</td>
</tr>
<tr>
<td><em>H. pylori</em></td>
<td>14 (18.7)</td>
<td>414 (21.6)</td>
<td>418 (21)</td>
</tr>
</tbody>
</table>

BE: Barrett’s esophagus, m: male, f: female, SD: standard deviation.

1,990) of individuals who underwent upper endoscopy for any symptoms except GERD. In addition, EE was observed in 11.1% of the same population and reflux symptoms were reported in 77.3% of patients with BE; thus, 22.7% (17 of 75) of patients with BE and 14 patients with EE, in total 31 participants (1.6%), were asymptomatic. In contrast to AC of the esophagus, the incidence and prevalence of BE are not known with precision. Studies report BE in approximately 6-12% of patients undergoing endoscopy for symptoms of GERD and in 1% or less of unselected patient populations undergoing endoscopy; the general prevalence of BE is estimated at 1.6-3% and follows a demographic distribution similar to AC and the rate of progression from BE to AC is 0.5% per patient-year. Furthermore, large variations among studies reporting BE prevalence around the world have been documented. Specifically for Greece, only 3 studies report data regarding BE prevalence. The first one detected specialized intestinal metaplasia in 26.7% of patients with GERD who prospectively underwent endoscopy for this reason. In the second study, a prevalence of BE of 3.5% was reported in a population undergoing diagnostic upper endoscopy. However in this study, this percentage was reached after staining with methylene blue for targeted biopsies, a procedure not routinely carried out. More recently, Chatzopoulos et al, in a prospective study that demonstrated the expression of markers Bax, Bcl-2 and Ki-67 in BE, reported a BE prevalence of 11.48% in a cohort of patients who underwent upper endoscopy for reflux symptoms. Therefore, to the best of our knowledge, this is the first study reporting the prevalence of BE as well as EE, GERD and silent GERD in a Greek cohort of patients who underwent upper endoscopy for indications other than reflux symptoms.

In our study, the prevalence of BE was 11.7% and 11.3% for patients with and without GERD symptoms, respectively. Comparably to our own latter finding, the prevalence of BE for patients without GERD symptoms undergoing endoscopy was also reported to be about 1-3%. Others reported that the prevalence of BE was 8.3% and 5.6% for patients with and without GERD symptoms, respectively. In a recent Veterans’ Affairs study with patients undergoing sigmoidoscopy for colorectal cancer screening, BE was detected in 25% of asymptomatic male veterans older than 50 years old. Several factors could have contributed to this high prevalence, including male predominance, older age, and a high percentage of Caucasians. Our population was Caucasian, thereby probably explaining the relatively high percentage of BE in patients with GERD symptoms.

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In this study four patients (5.3% of BE, a prevalence of 0.2%) were found with LSBE and 71 (94.7% of BE) with SSBE. Studies on BE showed that the prevalence of SSBE varies from 0.1% to more than 20% while the prevalence of LSBE varies from 1-2%; this variation may be due to geographical differences. Specifically, in Western countries, the prevalence of LSBE among patients undergoing endoscopy for any reason has been reported as 0.73% and 1.6% in two studies from North America, 1.9% in Australia, and 0.74% in Italy. In a more recent western study a higher prevalence of LSBE was reported with a BE length of > 4 cm in 35% of patients. However, this was a selected patient group; all patients with BE length < 2 cm were excluded from the study. In the Far East, where GERD is thought to be increasing in frequency, a study from Japan and one from Malaysia reported a LSBE prevalence of 0.62 and 1.6%, respectively. In a Turkish study, a neighboring country with similar eating habits, LSBE was reported in 0.8% of 1000 consecutive patients referred for endoscopy for any clinical indication. Our population study was characterized by the fact that patients referred for GERD were excluded from the study; thereby lower percentages of LSBE (0.2%) and SSBE (3.5%) were rather expected. In the study by Rex et al, screening for BE among patients undergoing colonoscopy, a population similar to ours in terms of indications, demonstrated a prevalence of 1.2% and 5.5% for LSBE and SSBE, respectively. This difference in results might be explained by the fact that their population was older, since patients over 40 were recruited. Furthermore, no data regarding population BMI were provided in their study, a parameter expected to be higher in older populations.

Several considerations are relevant to decisions regarding whether patients without reflux symptoms who have small tongues of columnar lined oesophagus should undergo biopsy for BE. These include the large number of such persons encountered in clinical practice, the overall low incidence of esophageal AC in the population, the possibility that SSBE is less important than LSBE as a risk factor for esophageal AC, and the limited cost-effectiveness of surveillance endoscopy in BE patients at currently recommended intervals. As aforementioned, we herein report a prevalence of SSBE that reaches 3.5% in a population not referred for GERD symptoms. Although these results are somehow alarming, whether SSBE has an increased cancer risk is poorly defined. Therefore, we believe that further relative large-scale studies are needed to establish that biopsy specimens from tongues, particularly of SSBE, in persons undergoing endoscopy for reason other than screening for BE in the setting of acknowledged esophageal AC risk factors, should be meticulously obtained.

An once-in-a-lifetime endoscopy has been debated for individuals with chronic typical reflux symptoms to identify BE and try to reduce the AC risk, particularly in the elderly. Published guidelines support the suggestion that patients who have experienced GERD symptoms for 5 years without alarm features should undergo endoscopy to exclude BE. Although, this strategy has been followed by most gastroenterologists in Greece, however it remains unclear whether this adds to BE-related AC prevention since, as mentioned before, AC prevalence remains relatively low (3.5 per 100,000 person-years: WHO 1995). Likewise, in the present series, low-grade dysplasia of BE was noticed in only one patient with LSBE and in
none with SSBE, whereas no case of high-grade dysplasia was documented in our patients with BE.

In this study, 2.07% of patients without GERD symptoms (22.6% patients with BE and 6.33% patients with EE) suffered from silent GERD. Although the pathogenesis of silent GERD is still not known, hyposensitivity to reflux of acid might possibly explain the condition\(^{39}\). However, the risk factors and clinical and prognostic implications of silent GERD remain unclear\(^{45}\).

Several investigations have identified the clinical features and characteristics of patients with BE. Age over 40 years, male gender, more frequent reflux episodes, the presence of a HH, increased BMI, and increased abdominal circumference have been associated with BE\(^{35,44-46}\). Although there was a trend for older age in the BE group, we did not find any significant difference in age between patients with and without BE. This finding has been reported in the past by other investigators\(^{36}\). A possible explanation is that we did not screen patients with GERD; therefore, our population was in general somewhat older. In our daily routine we screen young patients only if they have a very long duration of symptoms, they are non-responsive to PPIs or if they have alarm symptoms such as dysphagia, weight loss, or anemia. On the contrary, it is likely that patients over 50 years will be offered an upper endoscopy after a shorter duration of symptoms. Moreover, we found no difference in mean BMI, tobacco or alcohol use between patients with and without BE. Although it is hypothesized that alcohol consumption may increase the risk of BE indirectly by increasing the frequency of GERD, findings from recent studies are conflicting; some studies have reported no association with BE\(^{37,48}\), others have reported inverse associations with wine consumption\(^{49,50}\) and positive associations with total alcohol\(^{50}\) and liquor consumption\(^{51}\). These studies did not collect information on lifetime alcohol consumption and may be subject to misclassification and information bias, resulting from recent changes in alcohol intake. One recent study estimated the impact of lifetime alcohol consumption in the risk for BE\(^{52}\). In this study, comparably to our data, no evidence was found that total alcohol consumption or specific alcoholic beverages increased BE risk. Certainly, additional research is needed to confirm the aforementioned associations and clarify the mechanisms by which dietary components affect the risk of BE development and its consequences.

In the present study we did not find any correlation between BE and the presence of *H. pylori*. It is important to note that *H. pylori* status was determined by using the CLO-test on just one antral biopsy specimen for each participant. We acknowledge this as a limitation since it has been recommended that a CLO-test should be performed followed by histological examination if the CLO-test is negative to ensure adequate sensitivity. Specifically the CLO-test has a lower detection rate for *H. pylori* in the presence of mucosal atrophy and intestinal metaplasia. However, interpretation of histological slides has significant interobserver variability even in experienced hands and may be inaccurate at times. In contrast, increasing the number of antral biopsies from 1 to 4 significantly improves the sensitivity of the CLO-test, eliminates sampling error, and hastens the time needed by the test to become positive for the diagnosis of *H. pylori* infection\(^{53}\). Therefore, our series, by introducing the invasive CLO-test on one antral biopsy specimen for each patient, might underestimate the overall prevalence of *H. pylori* status in BE patients and controls.

*H. pylori* infection plays an etiological role in gastric carcinogenesis, but any potential role in esophageal disease, including BE is still controversial. Data from existing studies are conflicting, some demonstrating\(^{54,55}\) a protective effect of *H. pylori* infection against the development of GERD and BE, whereas other studies\(^{56}\) suggesting that the presence of *H. pylori* does not alter the natural history of BE. To date, three meta-analyses\(^{57-59}\) have reviewed the prevalence of *H. pylori* infection in BE and found that the prevalence of *H. pylori* infection was significantly lower in BE than in controls. These studies were heterogeneous; the first two metaanalyses\(^{57,58}\) mixed a variety of controls (including GERD patients and patients with a variety of diseases) whereas the third\(^{59}\) selected studies with healthy controls (endoscopically assessed or healthy blood donors). However they all concluded that to determine more accurately the effect size of *H. pylori* infection in BE, high quality prospective case-control studies with age-matched, endoscopically normal healthy controls are needed.

There is concern as to whether the prevalence of EE and BE in this study represent the prevalence in the general Greek population. Our study sample was biased toward persons undergoing upper endoscopy, who are more likely to have more gastrointestinal symptoms than the general population and who may have GERD symptoms more frequently. However, all 1990 individuals in our study were either self-referred or referred by other physicians/departments with indications other than reflux symptoms. Therefore, we believe that our results do reflect, to a considerable extent, the prevalence of BE and GERD, including silent GERD, in the general population. Nonetheless, further large scale epidemiologic study in the general population is required to confirm our hospital-based population. Another limitation is that magnification or “zoom” endoscopy as well as chromoendoscopy could have been useful in this study in directing biopsies for intestinal metaplasia. However, in a metaanalysis, the use of methylene blue chromoendoscopy for detecting specialized intestinal metaplasia and dysplasia in BE was not shown to have a superior diagnostic yield over random biopsies\(^{60}\). In contrast Narrow Band Imaging (NBI) is one method of high-resolution endoscopic imaging with application of the optical characteristics of light for the detection of mucosal and vascular details that has been demonstrated to accurately predict histology during screening and surveillance of BE patients\(^{61,62}\). BE (endoscopically identified “tongues”) was suspected in 224 patients during endoscopy but was...
finally diagnosed in only 75 participants who met both endoscopic and histological criteria for BE (intestinal metaplasia identified on histologic evaluation). Previous studies showed a poor correlation between endoscopic findings and histology\(^{7,8}\). Histologically identifiable BE has been detected in 25-32% of cases of short-segmental suspected columnar-lined esophagus and in 55% of cases of long-segmental suspected columnar-lined esophagus in random biopsies\(^{4}\). Furthermore, we cannot exclude the possibility that sampling error caused failure to identify BE in some of these patients.

In conclusion, the present study demonstrated a 3.77% frequency of BE in Greek patients undergoing upper endoscopy for symptoms other than GERD. HH and EE were independent risk factors for BE in GERD patients. In contrast, alcohol consumption, smoking and BMI were not associated to risk for BE. These findings, given the rising incidence of BE, may be useful to understand the interplay of dietary and environmental factors that influence the development of BE and its consequences.

**Conflict of Interest**

The authors declare that they have no conflict of interest.

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