Abstract. Background: Esophageal adenocarcinoma results from gastroesophageal reflux and develops along a sequence involving non-dysplastic Barrett’s esophagus (NDBE), low-(LGD) and high-grade dysplasia (HGD). We aimed to examine the reported annual cancer risk for NDBE in persons with symptoms of gastroesophageal reflux disease, i.e. symptomatic NDBE. Materials and Methods: Our study reviewed seven population-based studies and five meta-analyses on the annual cancer risk of symptomatic NDBE published between 2006-2012. Results: The published annual cancer risk of symptomatic NDBE ranges from 0.12-0.5% and 0.33-0.7% in population-based studies and meta-analyses, respectively. Risk factors for cancer development include male gender, age >60 years, length of endoscopically visible columnar lined esophagus (CLE) >3.0 cm, size of the hiatal hernia, progression to LGD/HGD and past history of cigarette smoking. The mean time-to-cancer development is 5 years and ranges from 2 to 15 years. Age at the diagnosis of symptomatic NDBE and cancer development plateaus around 50 and 60 years of age, respectively. Symptomatic NDBE does not affect the life expectancy, when compared to the general population. The majority of patients with NDBE do not die due to esophageal adenocarcinoma but due to comorbidity (cardiorespiratory, neurological, other cancer). The risk and prognosis of asymptomatic NDBE remains unknown. Conclusion: The published annual cancer risk for symptomatic NDBE is low. However, demographic and endoscopic data contribute to define a subgroup of patients with symptomatic NDBE with a cancer risk comparable to LGD, where elimination within controlled trials seems justified (radiofrequency ablation). Future efforts should extend towards asymptomatic NDBE, the major cause for cancer development.

Gastroesophageal reflux disease (GERD) affects 20-30% of the population (1). Due to the symptoms, GERD impairs quality of life and productivity (2). Furthermore, reflux inflames the esophagus (3). The inflammation triggers a complex neurohumoral reaction (4), which mediates the replacement of the normal squamous epithelium-lined mucosa with columnar-lined esophagus (CLE) (5-13): this is termed cardiac mucosa (CM) (14-17) (Figure 1A-D). CM may transform either to oxyntocardiac mucosa (i.e. CM with parietal cells within the subfoveolar region of the glands) or progress to intestinal metaplasia (IM), where the mucosal glands contain goblet cells (13, 17). A mixture of squamous epithelium and columnar epithelium defines the multilayered epithelium (MLE), which is frequently assessed in biopsies obtained from the squamo-columnar junction (15). Over time, CLE extends in length and becomes endoscopically visible (CLEv) (13, 14, 18-24) (Figure 1A and B). Recent animal studies indicate the involvement of bone marrow-derived stem cells in the development of CLE with and without IM (12).

While the presence of any type of CLE (CM, oxyntocardiac mucosa, OCM, IM) define non-dysplastic Barrett’s esophagus (BE) in Great Britain (25), the presence of CLE with goblet cells (IM) defines BE in North America (USA, Canada) and in most European countries (13, 14, 21-24) (Figure 1D). For the purpose of practicability and since the majority of studies use this definition, the presence of CLE with IM (goblet cells) defines BE in this article (Figure 1D). The presence of IM within endoscopically visible CLE <3.0 cm and ≥3.0 cm defines BE of short (SSBE) and long segment (LSBE), respectively (20, 21, 23). BE (CLE+IM) affects 20-30% of individuals with symptoms of GERD (18, 23). Endoscopic studies of patients with GERD revealed that in the absence of
CLE\textsubscript{v} (i.e. normal esophagogastric junction; EGJ) the frequency of BE ranges between 10% and 17% (14, 18). With greater length of CLE\textsubscript{v} (i.e. >5.0 cm) the frequency of IM increases towards 100% (18, 23, 26, 27). The frequency of BE within the normal population is variously reported as being 1.6% (28), 5.5% (29), 16% (18) and 25% (30).

BE deserves attention because it is a known risk factor for the development of esophageal adenocarcinoma, the frequency of which has increased dramatically during the past decades in Europe and North America (31, 32). Via a sequence involving low- (LGD) and high-grade (HGD) dysplasia, non-dysplastic BE (NDBE) may progress towards adenocarcinoma (13, 18, 22, 23). Indefinite dysplasia defines a condition, where, due to the inflammation, the pathologist cannot differentiate between CM or dysplasia (18-20). Re-endoscopy with biopsy sampling after a two-week treatment course with high-dose proton pump inhibitor (PPI, i.e. 2 ×40 mg daily) is recommended (18). Time from NDBE to cancer development ranges from 5 to 15 years (33-43).

Endoscopic screening for BE currently involves only those with symptoms of GERD and serves to detect those at increased risk for cancer development (i.e. those with NDBE, LGD, HGD) (18, 24).

Cancer develops along a multistep sequence of morphological changes, i.e. CM, NDBE, LGD and HGD. Surveillance offers the opportunity to assess and eliminate pre-malignant tissue before it turns into cancer (24). Discrepancy exists at which stage of the sequence from NDBE to HGD (i.e. early cancer) the physician should become active (23, 24). In addition to the family history, age, duration of GERD symptoms, length of CLE\textsubscript{v}, size of the hiatal hernia and gender (males are at greater risk for cancer development) (33-43), the annual cancer risk of NDBE, LGD and HGD serves as the basis for treatment decisions for BE, i.e. surveillance vs. removal (23, 24). Therefore, this review aims to summarize our current understanding regarding the reported annual cancer risk of BE in persons with symptoms of GERD, i.e. symptomatic NDBE.

Materials and Methods

The PUBMED search included data obtained from recent population-based follow-up endoscopy studies (years: 2006-2012) (25, 33-38) using search terms: “Barrett’s esophagus” AND “annual cancer risk” AND “dysplasia” AND “GERD” AND “esophageal adenocarcinoma”. In addition, we included published meta-analyses on the annual cancer risk of BE (years 2007-2012) (39-43). The presence of CLE with goblet cells within esophageal biopsies (IM) defined BE in all studies (33-38) except one from the UK (25), where CLE with/without goblet cells defined BE. Dysplasia was defined according to the Vienna classification (37, 38). CLE\textsubscript{v} indicates the proximal dislocation of the squamo-columnar junction (SCJ) above the level of the rise of the longitudinal gastric-type folds (rugae) (14, 16-18, 36-38) (Figure 1A and B). Hiatal hernia describes the proximal dislocation of the rise of the gastric-type folds above the level of the diaphragmatic impression during endoscopy (14, 16, 17, 37, 38).

We also considered novel concepts of esophageal anatomy, i.e. the dilated distal esophagus and the squamo-oxyntic gap (SOG), as described by Chandrasoma et al. (26, 27). Briefly, the dilated distal esophagus (DDE) is the reflux-damaged dilated portion of the distal esophagus, i.e. the cardia (26). The longitudinal folds of the DDE are entirely covered by CLE. As a result, the DDE gains an endoscopic gastric-type appearance (26). Consequently, the cardia is usually taken for the proximal stomach during endoscopy (3, 21). The SOG describes the reflux-induced morphology of the esophagus, with CLE interposed between the SCJ and the proximal limit of the oxyntic mucosa of the stomach (27). By definition, the SOG comprises the endoscopically visible CLE within the tubular esophagus and the dilated distal esophagus (cardia) (26, 27). Endoscopy assesses the proximal limit of the gap, i.e. the SCJ (3, 13, 16-18, 26, 27). The endoscopic appearance of the dilated distal esophagus resembles that of the proximal stomach (longitudinal folds covered with a columnar lined mucosa) (17, 26, 27). Therefore the fusion of histopathology and biopsy location of multi-level biopsies obtained from the endoscopic EGJ serves to define the distal limit of the gap and the DDE, i.e. the transition from CLE to the oxyntic mucosa of the proximal stomach (14, 17, 26, 27).

Here we reviewed seven population-based studies (25, 33-38) and five meta-analyses (39-43) on the annual cancer risk for NDBE and NDBE/LGD (25, 33-37), and LGD (38). In all studies, GERD symptoms were the indication for endoscopy, i.e. symptomatic NDBE. Annual cancer risk referred to the incident cases, i.e. cases that were detected more than one year after the initial diagnosis of NDBE and/or LGD (25, 33-36). Prevalent cases were HGD and/or adenocarcinoma, present at the endoscopy index or detected within the first year of surveillance (the ‘1-year rule’) (25, 33-38). Prevalent cases were excluded from the annual cancer risk analysis (25, 33-38). Only incident cases were used to calculate the annual cancer risk. The studies assessed the annual cancer risk of NDBE ‘cancer’ and the combined events ‘HGD and cancer’.

Statistics were not applied. Hazard ratio (HR) and confidence interval (CI) are depicted, as presented in the respective articles.

Results

Population-based studies. We first reviewed recent population-based studies on the annual cancer risk of NDBE and NDBE/LGD (Table I).

The multicenter Veteran’s hospitals study by Sharma et al. (33) included 1376 patients (83% men; age=59±12.3 years) with NDBE; with follow-up of 4.12 (range=1-22.5 years, a total of 2546 patient-years’ follow-up). The annual cancer risk for the progression of NDBE to LGD, HGD and cancer was 4.3%, 0.9% and 0.5%, respectively. The mean time to cancer development was 5.3 (2.4-11.2) years. The mean time to HGD development was 3.8 (1.2-7.9) years.

The recent population-based study from Northern Ireland by Bhat et al. (25) included 8522 patients with BE (age not presented, only available for the entire group of 9334 patients before exclusion of prevalent cases=60.9±15.5 years); 46% had CLE with IM, 54% had CLE without IM; (i.e. CM, OCM). The mean follow-up was 7.0 years (max.
For all CLE (with/without IM), the incidence for cancer and cancer/HGD development was 0.16% and 0.22% per year, respectively. The annual cancer risk for progression of CLE with IM to cancer and cancer/HGD was 0.27% and 0.38%, respectively. The annual cancer risk for CLE without IM (i.e., with CM, OCM) was 0.07%. Although cancer/HGD incidence was significantly higher in men (hazard ratio, HR=2.11 for HGD/cancer in men vs. women), events peaked at the age of 60-69 years for both sexes. The presence of LGD (HR=5.67) and long segment BE (HR=2.31) were associated with increased risk for the development of cancer/HGD. Presence or absence of CLE, did not affect the cancer/HGD risk.

The nationwide population-based study by Hvid-Jensen et al. (34) included the entire Danish population (5.4 million individuals) and identified 11028 patients with BE [66.8% males; age=62.7 (52.3-73.0) years; duration of the study: 1992-2009]. Cancer of the cardia was excluded. The median follow-up was 5.2 (2.8-8.9) years (total of 67.105 patient-years’ follow-up). The authors did not provide information on the outcome of the patients after the 5 years’ follow-up (death related to cancer or non-cancer related causes) and this is a limitation of the 17-year-long study.

The annual cancer risk for prevalent/incident and incident cancer (33.5%) was 0.29% and 0.12% per year, respectively. The annual incidence rate for HGD and HGD/cancer was 0.07% and 0.12% per year, respectively.
0.19% and 0.26%, respectively. Risk factors for cancer development included male sex (3.0-fold increased risk), age (highest for those older than 70 years) and LGD (3.0-fold increased risk). The median age at diagnosis of NDBE was 62.7 (52.3-73.0) years. The median time-to-cancer development was 4.8 (2.5-8.4) years, thus the median age at the time of cancer diagnosis was 68 (58.5-78.3) years. The median time of diagnosis of HGD and age of patients with HGD was 4.7 (2.4-8.3) years and 68 (58.4-78.3) years, respectively. A striking finding of the study was that the identified carcinomas during surveillance of NDBE only comprised 7.6% of all adenocarcinomas detected in Denmark during the study period (34).

The study by De Jonge et al. (35) included all cases of NDBE of the Dutch nationwide registry from 1991-2006 with follow-up until November 2007. The study included 42207 patients with NDBE (66% males). Patients with NDBE were significantly younger than those with LGD (61±15 years vs. 64±14 years). More men had NDBE and LGD at a younger age, when compared to women.

Follow-up data were available for 16,365 persons with NDBE (39%). The mean follow-up was 4.8 (SD=3) years with a total of 78131 patient-years; follow-up included 43568 endoscopies, on average 3 per patient (1-22). Cardia carcinomas (n=5) were excluded from the analysis. The annual incidence for cancer and cancer/HGD development was 0.43% and 0.58%, respectively. With the inclusion of all patients (with/without follow-up endoscopies; 42,207 patients; 234821 patient-years), the annual risk for cancer and HGD/cancer development was 0.14% (0.19% for males and 0.08% for females). Risk factors for progression of NDBE to cancer/HGD included male sex, older age (>60 years with HR=3.57) and LGD.

The population-based cohort study by Jung et al. (36) examined the outcome of NDBE in the Olmsted County population, Minnesota, USA (120000 inhabitants; 89% whites). Most importantly, the study compared the prevalence of IM, LGD, HGD, and cancer, and the annual HGD/cancer risk for IM within CLEv vs. IM within an endoscopically-normal appearing EGI (i.e. absence of CLEv) (36).

The study included 487 baseline cases of NDBE (401 cases with CLEv; 86 at a normal-appearing EGI; study period: 1976-2006; 30 years). Baseline IM at an endoscopically-normal EGI (i.e. no CLEv) was not associated with HGD and cancer, whereas 3% and 9% of those with CLEv at index endoscopy, had HGD and cancer, respectively. IM without CLEv was more frequent in females and those who did not consume alcohol. Furthermore, the condition was less often associated with heartburn, hiatal hernia and LGD when compared to NDBE within endoscopically-visible CLE (CLEv; 7% vs. 13%). Those with IM at a normal EGI had significantly less body weight (81±18 kg vs. 86±20 kg); body mass index was similar in the two groups.

A total of 355 patients were followed; those with HGD/cancer development within the first six months of follow-up were excluded from further calculations. The median follow-up was 8.0 years (1 month-17 years) and 7.8 years (2 days to 27 years) in those with IM without and with CLEv, respectively. The annual incidence for cancer was 0.29% and that for the combined HGD/cancer development was 0.79%, respectively. During the 8-year follow-up period, none of the individuals with IM at a normal EGI developed
CLE\textsubscript{v} and cancer. Thus all carcinomas developed in the CLE\textsubscript{v} group. Risk factors for progression of NDBE/LGD to HGD and cancer included previous alcohol use (HR=3.45) and past smoking (HR=4.57). Most probably due to the small number of patients, the increased length of CLE\textsubscript{v} of more than 3.0 cm did not become a significant risk factor (HR=3.93). Finally, the life expectancy of those with IM with/without CLE\textsubscript{v} was comparable to the age and sex distributed Minnesotan white population. Thus BE did not impair survival. The majority of patients with BE died due to cardiorespiratory, or neurological diseases and other types of cancer (lung, prostate, head and neck, renal). Only 5% of those with IM CLE\textsubscript{v} died as a consequence of esophageal cancer. None of those with IM at a normal EGJ died because of esophageal adenocarcinoma (36).

Wani et al. (37) conducted a multicenter study (BEST study) and included 1204 patients with NDBE (age=59.3±12.06 years; 88% males). The mean follow-up was 5.52 (±3.32) years for a total of 6644.5 patient-years. The length of CLE\textsubscript{v} was 3.8 (3.4) cm, 56.8% had a hiatal hernia of a mean size of 3.4 (1.84) cm. Annual cancer risk of NBDE was 0.27% (range within the centers from 0.2% - 0.4%). The mean time-to-cancer development was 5.29 (3.83) years (range=1.05-15.3 years). Annual risk of NBDE developing to HGD was 0.48% (mean time to HGD=5.6±1.7 years; range: 1.15-18.66 years). The annual risk of NBDE developing to HGD/cancer and LGD was 0.63% (inter-center range: 0.3%-1.2%) and 3.6%, respectively. Furthermore, 98.6%, 97.5% and 97.1%, of the patients with NBDE were cancer-free at 5, 8 and 10 years, respectively. In addition, 96.8%, 94.7% and 92.7% of the patients with NBDE were free of HGD/cancer at 5, 8 and 10 years, respectively. Age, smoking, use of aspirin, and hiatal hernia did not significantly affect the risk for progression to cancer. In contrast, CLE\textsubscript{v}, of ≥6.0 cm was associated with increased risk for progression to cancer and HGD/cancer.

Next, Wani et al. (38) summarized the annual risk of LGD to progress towards cancer or HGD/cancer. The study included 210 patients with LGD out of 2264 with NDBE (LGD patients: age=60.6±12.06 years; 97.9% whites, 85%, males) with a mean follow-up of 6.22±4.35 years (total of 959.6 patient-years). The authors assessed an hiatal hernia (mean length=3.74±2.0 cm) in 71% of the cases. There were 113 prevalent and 97 incident cases of LGD throughout the study period. Annual cancer risk of progression from LGD to cancer, LGD to HGD/cancer and LGD to HGD was 0.44%, 1.83% and 1.6%, respectively. The mean time from progression of LGD to cancer and HGD was 4.41±1.49 (3.34-7.05) years and 2.86±2.6 (0.18-10.07) years, respectively. At 3 and 5 years, 99.3% and 97.4% of the patients with LGD were free of cancer, respectively. At 3 and 5 years, 93.4% and 89.3% were free of HGD/cancer, respectively. According to the Kaplan–Meier survival graphs for all incident and prevalent cases of LGD, cancer and HGD/cancer developed at a frequency of 1.0% and 2% per year, respectively. Wani et al. (37) did not find a statistically significant difference in annual cancer risk between prevalent and incident cases of LGD. Most importantly, the study assessed the rate of inter-observer disagreement between central expert pathologists. The first and the second expert pathologist downgraded LGD in 19.3% and 17.0%, respectively and upgraded LGD in 12.5% and 19.3%, respectively (55.6% overall agreement).

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<th>Ref</th>
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Ref.: Reference number; FU: follow-up; PY: patient-years).

Meta-analyses. Next we summarized the results of recent meta-analyses assessing the annual cancer risk of NDBE (Table II). The meta-analysis by Thomas et al. (39) (41 studies; 11387 patients, 36635 patient-years’ follow-up) and Yousef et al. (40) (47 studies, 11279 patients, 47496 patient-years’ follow-up) reviewed studies published between 1984 and 2006 and found an annual cancer risk for NDBE of 0.7% (39) and 0.6% (40), respectively.

Out of 3843 citations, Rastogi et al. (41) included four studies published between 200-2005 with a mean follow-up between 3-7.3 years (1 multicenter study, 3 observational case series). The reviewed studies included 236 patients with 1241 patient-years’ follow-up. Based on the four studies, Rastogi et al. (41) calculated an annual cancer risk for NDBE of 0.57% (4.99%-8.46%).

Out of 7200 abstracts, Sikkema et al. (42) included 51 studies (64% males; age=61 years; 14109 patients; 61804
patient-years’ follow-up) and found an annual cancer risk of 0.63%. The cancer risk of BE varied between countries and was 0.63%, 0.65%, 0.56%, 0.65% in the UK, USA, non-UK European countries and Australia, respectively. The combined HGD cancer risk of BE was 1.2% (4528 patients; 22559 patient-years follow-up). A total of 19 studies reported on BE-induced mortality (7930 patients; 33022 patient-years’ follow-up) and found an annual risk for BE-related death due to cancer development of 0.3%; 17 studies (4207 patients; 24959 patient-years’ follow-up) showed that 7% and 93% of the patients died due to esophageal adenocarcinoma and other causes (cardiorespiratory, other malignancies etc.), respectively. Thus the annual risk of dying of non-cancer related causes was 3.71%.

A recent meta-analysis by Desai et al. (43) included 57 studies published between 1984 and 2011 (11434 patients, 58547 patient-years’ follow-up) and assessed an annual cancer risk for NDBE of 0.33%.

Discussion

The annual cancer risk of NDBE varies between countries and ranges from 0.12% to 0.5% and 0.33% to 0.7% in population-based studies and in meta-analyses, respectively (25, 33-43). Risk factors for cancer development include male gender, age >60 years, length of CLEv >3.0 cm, size of the hiatal hernia, progression to LGD/HGD and past history of cigarette smoking. The mean time-to-cancer development is 5 years and ranges from 2 to 15 years. The age at diagnosis of NDBE and cancer plateaus at around 50 and 60 years of age, respectively, leaving a gap of approximately 10 years for the detection of BE at the pre-malignant stage.

Differences regarding the size of the study population and years of follow-up are suggested to explain the heterogeneity of the reported annual cancer risk in the population-based studies (25, 33-38) and the meta-analyses (39-43). The reviewed studies indicate an inverse relationship between the annual cancer risk and the size of the study population. Cancer risk tends to decrease with an increased number of persons and patient-years of follow-up. The finding that the annual cancer incidence for NDBE varies between populations may justify every country establishing its individual population-based Barrett’s registry and documentation of the surveillance program.

At first sight, the cancer risk of NDBE appears to be extremely low and seems to be almost negligible (less than 0.7%) (Tables I and II). This is why many authorities recommend surveillance for NDBE and restrict endoscopic or surgical treatment for advanced disease (i.e. dysplasia, early cancer) (24, 33, 37, 43). However, annual cancer risk represents only one aspect of the entire problem. Incidence refers to the total number of patient-years of follow-up (24). Consequently this measure does not necessarily mirror the cancer risk of an individual. In contrast to that, inclusion of demographic, endoscopic, and histopathological data serve to more closely approximate the individual risk profile and help to tailor therapy. Accordingly, male gender, history of GERD symptoms of more than 10 years, positive family history for gastrointestinal cancer, increased length of CLEv (>3 cm) and the presence of a hiatal hernia increase the risk of progression of NDBE to LGD (25, 33-37, 44). Thus, the histopathology only describes one of numerous risk factors. Consequently the risk of NDBE varies depending on the entire individual risk profile. As a consequence, the treatment of NDBE should be tailored according to the individual risk profile. In line with this approach, radiofrequency ablation seems justified for those with NDBE and the above risk profile (44) i.e. high-risk NDBE.

A typical finding of our examination was that carcinomas of the cardia were excluded from the analyses (34-36) or that the studies did not indicate if adenocarcinomas of the cardia were considered in their calculations (25, 33, 37-43). Lagergren et al. (45) recently found that 29% of cardia carcinomas were associated with heartburn, regurgitation or both. Using well-defined anatomical and histopathological criteria, Chandrasoma et al. (26, 27) repeatedly demonstrated that cardia carcinomas arise within the distal portion of the SOG, i.e. the dilated distal esophagus, and thus represent esophageal cancer. Therefore, we cannot exclude omission of carcinoma of the cardia from contributing to underestimation of the annual cancer risk in the recent studies (25, 33-43).

At present, we do not know the size of the difference arising from the exclusion of cardia carcinoma from the investigations. However, it was recently demonstrated that the frequency of NBDE of the study by Ronkainen et al. (28) increased 10-fold by inclusion of IM of the dilated distal esophagus (18). Future studies should address this important issue and include the dilated distal esophagus, i.e. the cardia, in their calculations.

As a major drawback, all epidemiological studies on BE focus on the symptomatic population, i.e. those with symptoms of GERD (e.g. heartburn and regurgitation) (24). Consequently, screening for BE only includes symptomatic individuals. However, recent studies demonstrated that 40% and 71% of those with adenocarcinoma of the esophagus and the cardia, respectively, do not report a history of GERD symptoms (45). In addition, up to more than 90% of esophageal adenocarcinomas develop without a prior history of GERD symptoms (46). In line with these observations, Hvid-Jensen et al. (34) found that only 7% of esophageal adenocarcinomas were detected during the surveillance of patients with symptomatic NDBE. Furthermore, cancer detected during surveillance of symptomatic BE are of earlier tumor stage and are associated with longer survival (47). In
addition, up to 25% of asymptomatic individuals harbor NDBE (18, 30). These considerations question whether cancer prevention is adequately achieved by our current strategies. It seems justified to consider extending screening to the entire population and include those without GERD symptoms (24). In line with recent studies, esophageal endoscopy for both genders of 50 years of age has the highest yield for the detection of symptomatic NDBE (48). Future studies are to be designed to determine if this also holds true for asymptomatic BE. Surveillance and radiofrequency ablation should then be tailored according to the risk profile. Most importantly, our efforts should be documented within controlled trials. In addition, the impact and clinical relevance of novel screening tools is awaited (i.e. cytosponge) (49).

An interesting finding of the study by Jung et al. was that NDBE detected at a normal EGJ did not progress towards HGD/cancer during the 7- to 8-year follow-up period (36). The possibility remains that progression to cancer in this group of patients exceeds eight years. In addition, Bhat et al. (25) compared the cancer risk for NDBE and CM. The authors found that the annual cancer risk for NDBE and CM was 0.27% and 0.07%, respectively (25). Recent studies indicate that cancer does not develop without NDBE (22). In contrast to this, other authors suggest that cancer may directly arise from CLE without NDBE (i.e. CM) (21). It is possible that NDBE has been missed during the index and follow-up endoscopies in the study by Bhat et al. (25). We believe that the data justify including patients with NDBE-negative CLE in the surveillance at 5- to 7-year intervals (25). Finally, future studies with a follow-up of more than eight years should assess the outcome of NDBE at a normal appearing EGJ (36).

We found the annual cancer risk for symptomatic NDBE slightly decreased during recent decades. At present, we do not know the annual cancer risk of asymptomatic NDBE, the cause of the development of esophageal adenocarcinoma in up to 90% of cases (46). As a consequence, screening should be extended to individuals without GERD symptoms. The modern management of symptomatic NDBE should be based on the individual risk profile and include surveillance (47) and radiofrequency ablation (50, 51-53). Treatment of asymptomatic NBDE will be the focus of future studies.

References


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