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Magnitude and Time-Trend Analysis of Postendoscopy Esophageal Adenocarcinoma: A Systematic Review and Meta-analysis

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Abstract

BACKGROUND & AIMS: Identification of postendoscopy esophageal adenocarcinoma (PEEC) among Barrett's esophagus (BE) patients presents an opportunity to improve survival of esophageal adenocarcinoma (EAC). We aimed to estimate the proportion of PEEC within the first year after BE diagnosis.

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Conflicts of interest

These authors disclose the following: Rena Yadlapati has been a consultant for Medtronic, Ironwood Pharmaceuticals, and Diversatek, receives research support from Ironwood Pharmaceuticals, and is on the advisory board for Phathom Pharmaceuticals and RJS Mediagnostix; Siddharth Singh has received research grants from AbbVie and Janssen; David A. Katzka is an advisory board member of Celgene and Shire; and Sachin Wani is a consultant for Medtronic, Boston Scientific, Interpace, Exact Sciences, and Cernostics. The remaining authors disclose no conflicts.

This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e335. Upon completion of this exercise, successful learners will be able to define PEEC, determine the burden of PEEC post Barrett's endoscopy and apply quality measures to decrease PEEC.

Supplementary Material

Note: To access the supplementary material accompanying this article, please click here.

METHODS: Multiple databases (Medline, Embase, Scopus, and Cochrane databases) were searched until September 2020 for original studies with at least 1-year follow-up evaluation that reported EAC and/or high-grade dysplasia (HGD) in the first year after index endoscopy in nondysplastic BE, low-grade dysplasia, or indefinite dysplasia. The proportions of PEEC defined using EAC alone and EAC+HGD were calculated by dividing EAC or EAC+HGD in the first year over the total number of EAC or EAC+HGD, respectively.

RESULTS: We included 52 studies with 145,726 patients and a median follow-up period of 4.8 years. The proportion of PEEC (EAC) was 21% (95% CI, 13–31) and PEEC (EAC+HGD) was 26% (95% CI, 19–34). Among studies with nondysplastic BE only, the PEEC (EAC) proportion was 17% (95% CI, 11–23) and PEEC (EAC+HGD) was 14% (95% CI, 8–19). Among studies with 5 or more years of follow-up evaluation, the PEEC (EAC) proportion was 10% and PEEC (EAC+HGD) was 19%. Meta-regression analysis showed a strong inverse relationship between PEEC and incident EAC ($P < .001$). The PEEC (EAC) proportion increased from 5% in studies published before 2000 to 30% after 2015. Substantial heterogeneity was observed for most analyses.

CONCLUSIONS: PEEC accounts for a high proportion of HGD/EACs and is proportional to reduction in incident EAC. Using best endoscopic techniques now and performing future research on improving neoplasia detection through implementation of quality measures and educational tools is needed to reduce PEEC.

Keywords

Missed Esophageal Adenocarcinoma; Quality; Endoscopy; Surveillance

The incidence of esophageal adenocarcinoma (EAC) has been increasing over the past several decades with marginal improvements in mortality rates related to this lethal cancer.[1–3] Data using the Surveillance, Epidemiology, and End Results program of the National Cancer Institute showed a 7-fold increase in incidence from 1975 to 2016 (0.54 to 3.76 per 100,000 person-years).[2] To prevent death from this tumor, medical societies in countries around the world have recommended screening for and surveillance of Barrett's esophagus (BE)—the only identifiable premalignant condition for EAC.[4–7] Despite the considerable face validity of the current paradigm, several lines of epidemiologic data highlight the suboptimal impact of screening and surveillance strategies on population-based mortality from EAC.

Although colonoscopy is highly effective for the diagnosis and prevention of colorectal cancer (CRC), cancers can be diagnosed months or years after a colonoscopy that is negative for CRC or a CRC precursor lesions.[8] The World Endoscopy Organization recently addressed this important issue in colonoscopy quality by using an evidence-based consensus process to standardize terminology and definitions related to this phenomenon of postcolonoscopy colorectal cancer (PCCRC).[8,9] Similar to the phenomenon of PCCRC, there is increasing literature describing EAC that was missed in patients undergoing screening and surveillance for BE, clearly undermining the effectiveness of these practices.[1,8] To address this issue, the term postendoscopy esophageal adenocarcinoma (PEEC) was introduced in a recent document commissioned and approved by the American

Gastroenterological Association. PEEC was defined as EAC and/or BE-related high-grade dysplasia (HGD) identified within a finite time period of 1 year after a nondiagnostic endoscopy.[1]

Further understanding the magnitude of PEEC is the first critical step in the development of an evidence-based consensus to standardize PEEC terminology and calculation, potential explanations and measures to reduce PEEC in clinical practice, establish an infrastructure for future PEEC research, and potentially develop PEEC as a performance measure. A second step is determining if optimizing detection of PEEC will impact the pattern and occurrence of subsequent EAC incidence and survival. The aims of this systematic review and meta-analysis were to estimate the proportion of PEEC and its potential relationship to incident cancer among all cohort studies in adults with BE and conduct a time-trend analysis of PEEC over the past 3 decades.

Methods

Data Sources and Search Strategy

MEDLINE, EMBASE, Scopus, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews were searched by a medical reference librarian with the guidance of the study authors (T.S., D.A.K., and S.W.) until September 2020 for studies evaluating the detection of EAC after the initial BE diagnosis. The detailed search strategy is provided in Appendix 1. Additional references included in the previous meta-analysis[10] and known relevant studies also were examined for inclusion. Three investigators (T.S., A.M.M., and T.N.) independently reviewed the identified abstracts and selected reports for full review. Discrepancies between 2 reviewers were resolved by the third reviewer and by discussion with the senior investigators (D.A.K. and S.W.). If multiple studies originated from the same cohort, the study with the most comprehensive data was selected for inclusion.

Study Selection

Studies meeting screening criteria were included in this meta-analysis if they met the following specific criteria: (1) the cohort included patients with endoscopic and/or biopsy-proven BE (the definition provided by the included studies for BE was used with the majority defining BE as a columnar-lined esophagus with intestinal metaplasia); (2) the cohort included subjects with nondysplastic BE (NDBE), low-grade dysplasia (LGD) or indefinite for dysplasia (IND) at baseline; (3) reported mean/median follow-up period of at least 1 year from the time of BE diagnosis; (4) reported the detection rates of EAC or HGD during follow-up evaluation; and (5) provided data on the timing of detection of HGD and EAC after a negative index endoscopy to classify these cases as incident cases and PEEC. Studies were excluded for the following reasons: (1) cohort included fewer than 10 subjects; (2) there were insufficient data to determine the numbers of incident and PEEC cases; (3) BE cohorts included HGD or EAC cases at baseline, and outcomes for subjects with baseline NDBE, LGD, or IND could not be determined separately from HGD; (4) selective group that does not represent the general BE population (eg, women only, African Americans only); (5) cohort included patients undergoing surgery or endoscopic eradication

therapy (radiofrequency ablation, cryotherapy, endoscopic resection); (6) excluded patients who developed HGD or EAC within 1 year; (7) conference abstracts before 2019; and (8) reports without original data, review articles, letters to the editor, editorials, and animal and in vitro studies.

Data Extraction and Quality Assessment

For each selected study, key study characteristics were abstracted including publication year, country, study design, age, Barrett's length in centimeters or using the Prague classification when available, biopsy protocol (Seattle biopsy protocol vs random biopsy specimens), degree of dysplasia, surveillance protocol, and follow-up time. The number of PEEC cases was determined based on the timing of detection of HGD or EAC after the index endoscopy. If the time of EAC incidence was not reported but the Kaplan–Meier curve was provided, the number was estimated from the graph, taking into consideration cumulative proportions and patients at risk.

The methodologic quality of comparative cohort studies was assessed using a modified tool derived from the Newcastle–Ottawa Score.[10,11] The quality assessment tool consisted of 9 domains based on selection and outcome assessment and is described in Supplementary Table 1.

Study Definitions

EACs reported by cohort studies included in this analysis were divided into 2 categories: PEEC and incident EAC. We used 2 definitions to calculate PEEC based on the inclusion of HGD vs EAC alone. PEEC (EAC) was defined as EAC diagnosed within 1 year of a negative index endoscopy (in which BE was diagnosed). PEEC (EAC+HGD) was defined as a composite of EAC and HGD diagnosed within 1 year of a negative index endoscopy. Incident EAC was defined as EAC diagnosed more than 1 year after a negative index endoscopy. Incident EAC with HGD was defined as EAC and HGD diagnosed more than 1 year after a negative index endoscopy. The 1-year cut-off time was chosen because EAC and HGD diagnosed within the first year most likely were present during the index endoscopy and thus represent missed lesions.

Data Synthesis, Study Outcomes, and Statistical Analysis

The primary outcome was the proportion of PEEC (EAC), PEEC (EAC+HGD), and incident EAC among all EACs detected after a negative index endoscopy in BE patients with NDBE, LGD, and IND with at least 1 year of follow-up evaluation. Secondary outcomes included the proportion of PEEC stratified by baseline histology at the index endoscopy, and by follow-up duration. The proportion of PEEC (EAC) was calculated by dividing the number of EACs detected the first year after the index endoscopy over the total number of EACs. Similarly, the PEEC (EAC+HGD) proportion was calculated by dividing the number of HGDs and EACs detected in the first year after the index endoscopy over the total number of HGDs and EACs. The PEEC (EAC) proportions and PEEC (EAC+HGD) proportions and 95% CIs were pooled and weighted using the random-effects model. We used the Freeman–Tukey double arcsine method to assure that studies with zero events were not excluded. Heterogeneity among studies was assessed with the inconsistency index (I^2)

statistic, which ranges from 0% to 100% and is defined as the percentage of the observed inter-trial variability that is the result of heterogeneity rather than chance for each outcome. Time trends were calculated by pooling PEEC (EAC) and PEEC (EAC+HGD) proportions for each time period from 2000 and earlier, 2001 to 2005, 2006 to 2010, 2011 to 2015, and after 2015 based on the date of publication of the study and not when the endoscopy was performed for included patients. Individual level data on when the endoscopy was performed were not available and hence the publication date was used as a surrogate for this analysis. To further investigate the source of heterogeneity, multiple prespecified subgroup analyses were performed based on follow-up time (longer follow-up periods may lead to lower PEEC proportions), region of origin, baseline histology (higher proportion of LGD and IND may lead to higher PEEC proportions), biopsy protocol (studies that followed the Seattle protocol may have lower PEEC proportions), BE segment length (a longer BE segment will lead to higher sampling errors and higher PEEC proportions), and the quality of studies. We performed a Z test of interaction between the relative risk in each subgroup, which tests the null hypothesis that the effect in each subgroup is the same. We also performed a meta-regression to assess whether the effect estimates varied based on follow-up time. We examined the effect of each individual study on the overall results by omitting 1 study at a time to ensure no major study effect. Funnel plots and the Egger test were used to detect the possibility of publication bias. All statistical analyses were performed using STATA software 14.2 (College Station, TX). We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to report the results of this systematic review and meta-analysis.[12]

Results

Our literature search yielded 3515 studies; of which 52 studies met our inclusion criteria for the meta-analysis and reported outcomes in 145,726 BE patients (Figure 1).[13–64] The characteristics of the included studies are shown in Table 1. The majority of the studies originated from Europe (n = 28), North America (n = 20), or both combined (n = 2). With regard to the study setting, the majority were single-center studies (n = 30), followed by multicenter (n = 12) and population-based studies (n = 10). The mean/median follow-up period was 4.8 years and ranged between 1.2 and 14.9 years (interquartile range [IQR], 3.7–6 y); 20 studies reported a mean follow-up period of 5 years or longer. This analysis included 4 abstracts published in 2019 to 2020 while the rest were full peer-reviewed articles. Baseline histology was a mix of NDBE and LGD (28 studies); NDBE only (12 studies); a mix of NDBE, LGD, and IND (5 studies); LGD only (4 studies); and IND only (3 studies). Twenty-seven studies reported the biopsy protocol, of which 12 studies reported taking biopsy specimens using the Seattle biopsy protocol (biopsy specimens from 4 quadrants every 1–2 cm). Overall, the majority of included studies were of high (n = 13) or medium (n = 33) quality, with 6 studies considered low quality (Supplementary Table 2).

Postendoscopy Esophageal Adenocarcinomas Among All Barrett's Esophagus Cohorts

Among the 32 studies that reported the detection of EAC in the first year after the index endoscopy that diagnosed BE, the pooled proportion of PEEC (EAC) was 21% (95% CI, 13%–31%; I^2, 86.5%) (Table 2, Supplementary Table 3). The pooled proportion of PEEC

(EAC+HGD) among 42 studies was 26% (95% CI, 19%–34%; I^2, 93.4%). Because repeat endoscopy is recommended in 3 years after the index endoscopy for NDBE, we decided to restrict our analysis to studies with a minimum average follow-up period of 3 years. The pooled proportion of PEEC (EAC) (30 studies) was 18% (95% CI, 10%–27%; I^2, 83.8%). The pooled proportion of PEEC (EAC+HGD) (37 studies) was 23% (95% CI, 15%–31%; I^2, 92.8%). When restricting the analysis further to studies with follow-up periods of 5 years or longer, the pooled proportion of PEEC (EAC) (13 studies) was 10% (95% CI, 0%–32%; I^2, 90.9%). The pooled proportion of PEEC (EAC+HGD) with follow-up periods of 5 years or longer (16 studies) was 19% (95% CI, 7%–35%; I^2, 96%). On the other hand, when restricting the analysis to follow-up periods of shorter than 5 years, the pooled proportion of PEEC (EAC) (19 studies) was 28% (95% CI, 19%–39%; I^2, 80.5%) and PEEC (EAC+HGD) (24 studies) was 31% (95% CI, 22%–40%; I^2, 87.9%). On meta-regression, follow-up time significantly altered the PEEC (EAC) effect estimate ($P = .03$), but not the PEEC (EAC+HGD) ($P = .09$).

Time Trend

Time-trend analysis was performed based on the publication year of the included cohort studies. The PEEC (EAC) pooled proportion increased from 5% (95% CI, 0%–19%; I^2, 16.4%) in studies published in 2000 or earlier and 3% (95% CI, 0%–21%; I^2, 0%) in 2001 to 2005 to 30% (95% CI, 25%–35%; I^2, 0%) in 2006 to 2010, 46% (95% CI, 21%–72%; I^2, 73%) in 2011 to 2015, and 30% (95% CI, 16%–46%; I^2, 93.5%) after 2015. Similar results were noted in an analysis that assessed proportions of PEEC (EAC+HGD) (Figure 2). The median average follow-up period was 3.9 years (IQR, 3.6–4.8 y) in studies published in 2000 or earlier, 5.8 years (IQR, 4.8–9.6 y) in 2001 to 2005, 5 years (IQR, 3.7–5.5 y) in 2006 to 2010, 4 years (IQR, 3–5.2 y) in 2011 to 2015, and 4.8 years (IQR, 3.8–6.2 y) after 2015.

Relationship of Postendoscopy Esophageal Adenocarcinoma to Incident Esophageal Adenocarcinoma

To assess if the magnitude of PEEC had an effect on EAC incidence with surveillance, the log relative risk EAC found in PEEC (EAC) was plotted against the incidence EAC found after 1 year within individual studies (Figure 3). The meta-regression analysis showed a strong inverse relationship between PEEC and incident EAC ($P < .001$).

Subgroup Analyses

To explore the source of heterogeneity, multiple predefined subgroup analyses were performed based on region of origin, baseline histology, biopsy protocol, BE segment length, and the quality of studies (Table 2).

Region of origin.—The pooled proportion of PEEC (EAC) in studies from North America (n = 10; 15%; 95% CI, 2%–33%; I^2, 80.3%) was similar to those reported among European studies (n = 20; 25%; 95% CI, 15%–37%; I^2, 89.4%) ($P = .27$). Similar results were noted in an analysis that compared the proportion of PEEC (EAC+HGD) cases between the 2 regions (North America, n = 15; 26%; 95% CI, 14%–40%; I^2, 90.5%; vs Europe, n = 24; 29%; 95% CI, 21%–38%; I^2, 93.6%; $P = .38$).

Baseline histology.—When restricting the analysis to studies that included NDBE only, the pooled proportion of PEEC (EAC) (n = 8) was 17% (95% CI, 11%–23%; I^2, 3.6%) and PEEC (EACbHGD) (n = 10) was 14% (95% CI, 8%–19%; I^2, 13.3%). Compared with the studies that included NDBE only, the pooled proportion of PEEC (EAC) in studies combining NDBE and LGD (n = 19) was 19% (95% CI, 8%–32%; I^2, 90.1%; P = .14) and PEEC (EAC+HGD) (n = 20) was 25% (95% CI, 14%–36%; I^2, 95.8%; P = .15).

Biopsy protocol.—The pooled proportion of PEEC (EAC) in studies that described the use of the Seattle biopsy protocol for sampling (n = 8) was 29% (95% CI, 15%–45%; I^2, 22.2%) compared with those that did not report using this biopsy protocol (n = 24) of 20% (95% CI, 11%–31%; I^2, 89.6%; P = .42). The pooled proportion of PEEC (EAC+HGD) in studies that described the use of the Seattle biopsy protocol for sampling (n = 11) was 33% (95% CI, 17%–51%; I^2, 83.9%) compared with 24% (95% CI, 16%–32%; I^2, 94.5%) in those that did not report the use of this protocol (n = 31; P = .05).

Length of Barrett's esophagus segment.—The pooled proportion of PEEC (EAC) in studies in which long-segment BE (LSBE) composed 50% or more of the cohort (n = 16) was 17% (95% CI, 8%–27%; I^2, 43.2%) compared with those that included less than 50% LSBE (n = 6), which was 13% (95% CI, 0%–34%; I^2, 48.2%; P = .41). The pooled proportion of PEEC (EAC+HGD) in studies that included 50% or more of LSBE patients (n = 19) was 22% (95% CI, 11%–36%; I^2, 94.3%) compared with those that included less than 50% LSBE patients (n = 10), which was 21% (95% CI, 6%–41%; I^2, 93.9%; P = .72).

Study setting: population-based studies vs referral centers.—The pooled proportion of PEEC (EAC) in population-based studies (n = 5) was 45% (95% CI, 30%–61%; I^2, 97.3%) compared with 13% (95% CI, 6%–22%, I^2, 43.3%) among studies that included referral centers (n = 27). PEEC (EAC+HGD) was 38% (95% CI, 26%–50%; I^2, 97.2%) in population-based studies compared with 21% (95% CI, 13%–30%; I^2, 84.7%) in studies conducted at referral centers (n = 32).

Quality of studies.—The overall rates of PEEC (EAC) and PEEC (EAC+HGD) were stable based on the quality of included studies. The pooled proportion of PEEC (EAC) among high-quality studies (n = 8) was 16% (95% CI, 5%–30%; I^2, 5%) and PEEC (EAC+HGD) (n = 12) was 23% (95% CI, 8%–42%; I^2, 85%).

Sensitivity Analysis

A sensitivity analysis performed by omitting 1 study at a time showed no excessive influence of 1 study on the overall results. Publication bias was assessed using funnel plot and the Egger test for small-study effects. There was no small-study effect on PEEC (P = .95) and PEEC with HGD (P = .17) (Figure 4).

Discussion

Similar to PCCRC, the concept of PEEC, largely driven by missed EAC, is gaining importance in endoscopic BE screening and surveillance. Determining true estimates of

PEEC in clinical practice can help determine intervention strategies to optimize outcomes related to current screening and surveillance strategies.

This systematic review and meta-analysis of 52 studies shows that PEEC accounts for nearly one quarter of all HGD/EAC diagnosed in BE patients. The proportion remained high at 22% when restricting the analysis to studies with follow-up evaluation longer than 5 years. These findings highlight the significant burden of missed HGD/EAC after the index endoscopy. The proportion of PEEC (EAC) remained high (17%) even among patients with NDBE at index endoscopy, who typically do not undergo a repeat upper endoscopy until 3 to 5 years. These results were stable across multiple a priori–defined subgroup and sensitivity analyses, based on study region, sampling technique, BE length, and study quality. Another key observation of this study was the increasing proportion of patients diagnosed with PEEC over the past 2 decades; the proportion of PEEC (EAC) has increased from 5% in studies published before 2000 to 30% in studies published in the past 5 years. Finally, we show that the prevalence of PEEC has a direct relationship to the subsequent development of incident EAC.

Similar to this study, a previous meta-analysis in 2016 that included 24 studies reported that nearly 25% of EACs are diagnosed within 1 year after the index endoscopy among patients with NDBE.[10] The impetus for updating this meta-analysis was the need to provide an updated estimate of PEEC using contemporary definitions and further assess the implications of finding PEEC on the overall incidence of EAC.[1] Notable differences include nearly twice the number of studies that were included in this analysis, elimination of publication bias, and the ability to conduct a time-trend analysis that showed an increase in the proportion of PEEC. Similar to the previous analysis, the proportion of prevalent EACs could not be determined owing to the inability to determine if EAC were detected during screening vs EAC detected in patients presenting with alarm symptoms (dysphagia, weight loss, iron-deficiency anemia). In a recent study using data from large commercial and Medicare Advantage health plans in the United States from 2004 to 2019, we identified 50,817 individuals with newly diagnosed BE and reported on proportions of individuals with prevalent EAC, PEEC, and incident EAC. Of the 366 patients who developed EAC, 67.2% were diagnosed with prevalent EAC and 13.7% were diagnosed with PEEC. These data add to the growing body of literature showing the high proportion of PEEC and that the prevalence far exceeds the incidence of EAC.[45,65]

One means of reducing PEEC might be referring patients with Barrett's after index endoscopy to expert centers. This is supported by finding a higher rate of PEEC in population (ie, community) studies. Unfortunately, this strategy has numerous limitations from a physician resource and patient point of view. As a result, it is hoped that similar to interventions used in colorectal screening and surveillance, systematic efforts to improve the quality of endoscopic detection of advanced neoplasia and EAC has the potential to decrease the proportion of PEEC considerably. Some proposed interventions include adequate time inspecting the BE segment (1 minute of inspection time per centimeter of circumferential BE),[66,67] use of high-definition white light endoscopy and virtual chromoendoscopy,[68] and adherence to the Seattle biopsy protocol.[69] It is expected that artificial intelligence and use of advanced sampling techniques such as wide-area transepithelial sampling will

reduce PEEC rates and should be the focus of future studies.[70,71] Further research is required to assess if completion of validated training courses that focus on the detection and delineation of BE-related neoplasia reduces PEEC.[72] Finally, establishing an infrastructure among endoscopy practices for continuous monitoring of upper-endoscopy quality in BE patients undergoing screening and surveillance and standardization of quality assessment may improve BE-related neoplasia rates. Similar to the adenoma detection rate in colon cancer, the neoplasia detection rate, defined as the prevalence of HGD/EAC within BE during the index screening endoscopy, has been proposed as a process quality indicator.[73,74] Recent data have shown an inverse relationship between the neoplasia detection rate and PEEC rates.[60] Furthermore, this study extends the meaning of PEEC further by showing an inverse relationship between PEEC and incident EAC found during surveillance. These data thus may have additional effects on allocation of resources for detecting HGD or curable-stage EAC. Future studies are needed to assess harder end points such as a decrease in EAC mortality and/or detection of EAC at earlier treatable stages throughout Barrett's surveillance when detection of PEEC is optimized.

There are several potential limitations to consider when interpreting these results. This meta-analysis includes results from multiple centers and the standardization of endoscopic examinations and biopsies cannot be ensured. The relationship between appropriate sampling using the Seattle biopsy protocol and PEEC needs to be explored in future studies. The reasons necessitating a repeat endoscopy were that diagnosed PEEC were not available and needed to be assessed in future prospective quality benchmarking studies. Another important limitation in drawing conclusions from this work is the substantial amount of heterogeneity; a finding that is not uncommon in studies assessing prevalence and proportions. Although this was resolved when restricting the analysis to NDBE only, this persisted with other subgroup analyses. Finally, this study was unable to provide any insight on the potential explanation for PEEC (missed HGD or EAC vs rapidly progressive cancer) with our assumption being that the majority of PEEC cases represent missed lesions during endoscopy. The contribution of rapidly progressive cancers to PEEC rates using phenotypic and epigenetic analysis needs to be addressed in future studies.[75,76] Finally, in performing our time-trend analysis we realize that endoscopies included in these studies may have occurred years before the publication date used in the analysis.

In conclusion, results of this systematic review and meta-analysis show a significant burden of PEEC in clinical practice with nearly 25% of HGD/EACs diagnosed within 1 year of a negative index endoscopy. Increasing rates of PEEC in recent years call for future research on interventions that focus on quality measures and educational tools designed to improve detection of BE-related neoplasia. At present, best practice recommendations such as adequate inspection time, use of high-definition white-light endoscopy in conjunction with virtual chromoendoscopy, and appropriate sampling of the BE segment should be implemented to reduce PEEC. Appraisal of the true magnitude of PEEC has laid the foundation for an evidence-based consensus study to standardize terminology, identification, analysis, reporting, and reducing PEEC in clinical practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix 1.: Search Strategies

Data Sources and Search Strategies

A comprehensive search of several databases from 2010 to September 11, 2020, limited to the English language and excluding animal studies, was conducted. The databases included Ovid MEDLINE and Epub Ahead of Print, In-Process and Other Non-Indexed Citations and Daily, Ovid Embase, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus.

The search strategy was designed and conducted by an experienced librarian with input from the study's principal investigator. Controlled vocabulary supplemented with keywords was used to search for studies describing missed esophageal adenocarcinoma after a Barrett's esophagus diagnosis. The actual strategy listing all search terms used and how they are combined is shown.

OVID

Database(s) included the following: Ovid MEDLINE(R) 1946 to Present and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Ovid MEDLINE Daily, EBM Reviews–Cochrane Central Register of Controlled Trials August 2020, EBM Reviews–Cochrane Database of Systematic Reviews 2005 to September 10, 2020, Embase 1974 to 2020 September 10. The search strategy was as follows:

#	Searches
1	"Barrett Esophagus"/
2	(barrett* or ((esopha* or oesophag*) adj1 (((“low-grade” or “low grade”) adj1 dysplas*) or nondysplas* or precancerous or “precancerous” or (precursor adj1 lesion*)))).ti,ab,kw.
3	Precancerous Conditions/ and (esophagus/ or (esopha* or oesophag*).ti,ab,kw.)
4	1 or 2 or 3
5	“Adenocarcinoma”/ and “Esophageal Neoplasms”/
6	((esophag* or oesophag*) adj1 adenocarcinoma).ti,ab,kw.
7	((esophag* or oesophag*) adj3 “high-grade” adj3 dysplas*).ti,ab,kw.
8	5 or 6 or 7
9	(miss* or repeat* or annual or yield* or risk* or surveillance or progress* or “follow-up” or early or diagnos* or detect* or recogniz* or recognis* or screen*).ti,ab,kw.

#	Searches
10	*Disease Progression/ or *Risk Assessment/ or *Risk Factors/ or *Follow-Up Studies/ or Early Detection of Cancer/ or Early Diagnosis/ or *Time Factors/ or Diagnostic Errors/
11	9 or 10
12	4 and 8 and 11
13	limit 12 to english language [Limit not valid in CDSR; records were retained]
14	limit 13 to yr="2010 -Current"
15	14 not ((exp animals/ or exp nonhuman/) not exp humans/)
16	remove duplicates from 15

SCOPUS

1	TITLE-ABS-KEY (barrett* or ((esopha* or oesophag*) w/1 (((“low-grade” or “low grade”) w/1 dysplas*) or nondysplas* or precancerous or “pre-cancerous” or (precursor w/1 lesion*))))
2	TITLE-ABS-KEY ((esophag* or oesophag*) w/1 adenocarcinoma)
3	TITLE-ABS-KEY ((esophag* or oesophag*) w/3 “high-grade” w/3 dysplas*)
4	2 or 3
5	1 and 4
6	INDEX(embase) OR INDEX(medline) OR PMID(0* OR 1* OR 2* OR 3* OR 4* OR 5* OR 6* OR 7* OR 8* OR 9*)
7	5 not 6
8	DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh) OR DOCTYPE(ch)
9	7 not 8
10	LANGUAGE(english)
11	9 and 10
12	PUBYEAR AFT 2009
13	11 and 12
14	(TITLE-ABS-KEY ((alpaca OR alpacas OR amphibian OR amphibians OR animal OR animals OR antelope OR armadillo OR armadillos OR avian OR baboon OR baboons OR beagle OR beagles OR bee OR bees OR bird OR birds OR bison OR bovine OR buffalo OR buffaloes OR buffalos OR “c elegans” OR “Caenorhabditis elegans” OR camel OR camels OR canine OR canines OR carp OR cats OR cattle OR chick OR chicken OR chickens OR chicks OR chimp OR chimpanze OR chimpanzees OR chimps OR cow OR cows OR “D melanogaster” OR “dairy calf” OR “dairy calves” OR deer OR dog OR dogs OR donkey OR donkeys OR drosophila OR “Drosophila melanogaster” OR duck OR duckling OR ducklings OR ducks OR equid OR equids OR equine OR equines OR feline OR felines OR ferret OR ferrets OR finch OR finches OR fish OR flatworm OR flatworms OR fox OR foxes OR frog OR frogs OR “fruit flies” OR “fruit fly” OR “G mellonella” OR “Galleria mellonella” OR geese OR gerbil OR gerbils OR goat OR goats OR goose OR gorilla OR gorillas OR hamster OR hamsters OR hare OR hares OR heifer OR heifers OR horse OR horses OR insect OR insects OR jellyfish OR kangaroo OR kangaroos OR kitten OR kittens OR lagomorph OR lagomorphs OR lamb OR lambs OR llama OR llamas OR macaque OR macaques OR macaw OR macaws OR marmoset OR marmosets OR mice OR minipig OR minipigs OR mink OR minks OR monkey OR monkeys OR mouse OR mule OR mules OR nematode OR nematodes OR octopus OR octopuses OR orangutan OR “orang-utan” OR orangutans OR “orang-utans” OR oxen OR parrot OR parrots OR pig OR pigeon OR pigeons OR piglet OR piglets OR pigs OR porcine OR primate OR primates OR quail OR rabbit OR rabbits OR rat OR rats OR reptile OR reptiles OR rodent OR rodents OR ruminant OR ruminants OR salmon OR sheep OR shrimp OR slug OR slugs OR swine OR tamarin OR tamarins OR toad OR toads OR trout OR urchin OR urchins OR vole OR voles OR waxworm OR waxworms OR worm OR worms OR xenopus OR “zebra fish” OR zebrafish) AND NOT (human OR humans OR patient OR patients)))
15	13 not 14

Abbreviations used in this paper:

BE	Barrett's esophagus
EAC	esophageal adenocarcinoma
HGD	high-grade dysplasia
I^2	inconsistency index
IND	indefinite dysplasia
IQR	interquartile range
LGD	low-grade dysplasia
LSBE	long-segment Barrett's esophagus
NDBE	nondysplastic Barrett's esophagus
PCCRC	postcolonoscopy colorectal cancer
PEEC	postendoscopy esophageal adenocarcinoma

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What You Need to Know

Background

Current Barrett's esophagus screening and surveillance practices have had a suboptimal impact on esophageal adenocarcinoma (EAC) outcomes. The concept of postendoscopy esophageal adenocarcinoma (PEEC) was introduced recently and is driven mainly by missed EAC or high-grade dysplasia (HGD) at index endoscopy.

Findings

The magnitude of PEEC accounts for nearly one quarter of EAC/high-grade dysplasia diagnosed during surveillance. The proportion of PEEC cases has been strikingly increasing over the past decades. There is a strong inverse relationship between PEEC and incident EAC.

Implications for patient care

These findings have laid the foundation for an evidence-based consensus study to standardize the terminology, identification, analysis, reporting, and reducing PEEC in clinical practice.

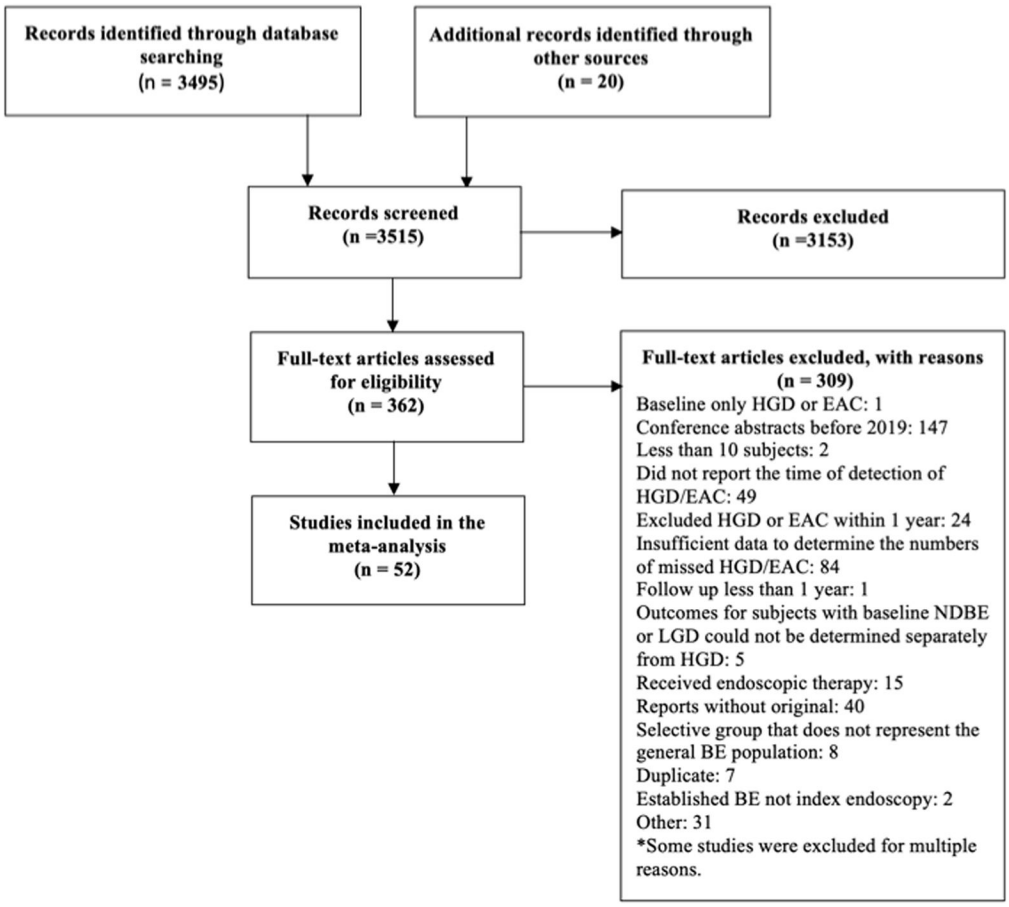

Figure 1.

Flow diagram of study selection. BE, Barrett's esophagus; EAC, esophageal adenocarcinoma; HGD, high-grade dysplasia; LGD, low-grade dysplasia; NDBE, nondysplastic Barrett's esophagus.

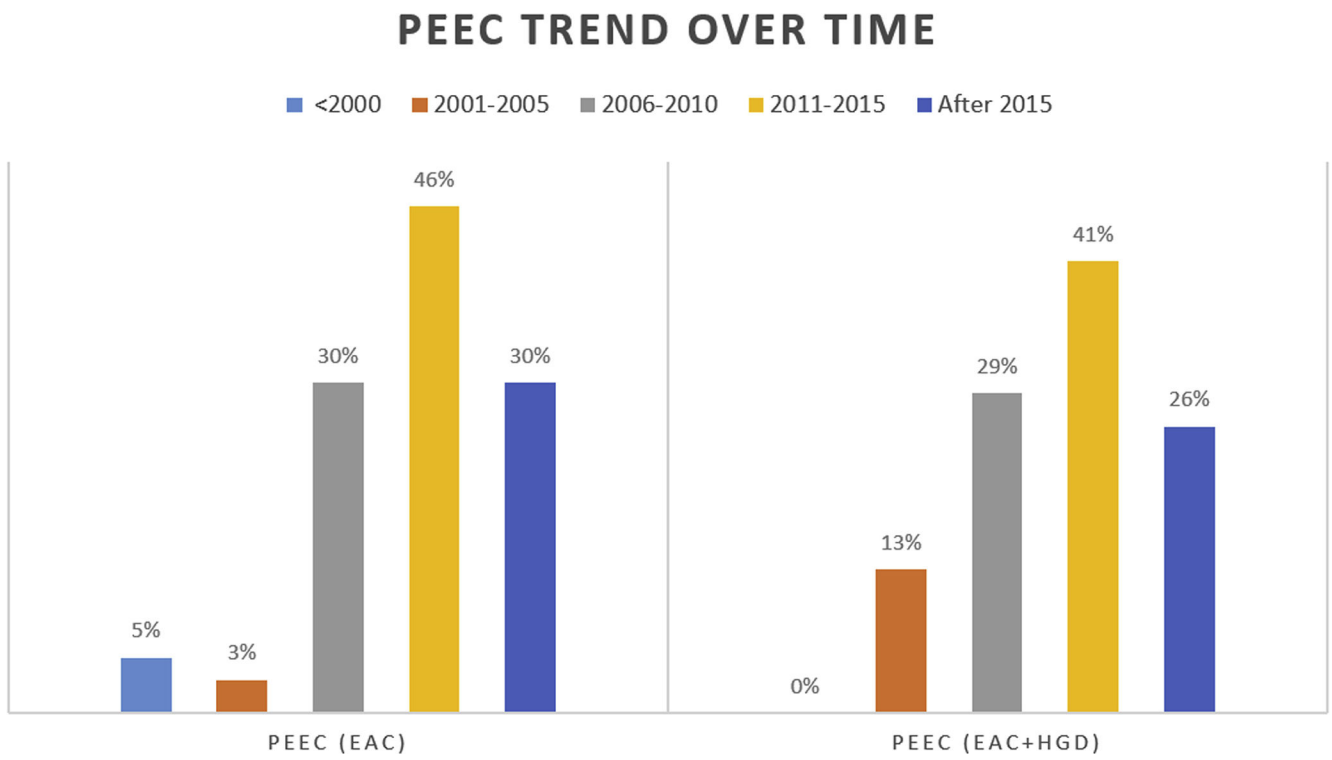

Figure 2.
The trend of postendoscopy esophageal adenocarcinoma (PEEC) proportion over time. EAC, esophageal adenocarcinoma; HGD, high-grade dysplasia.

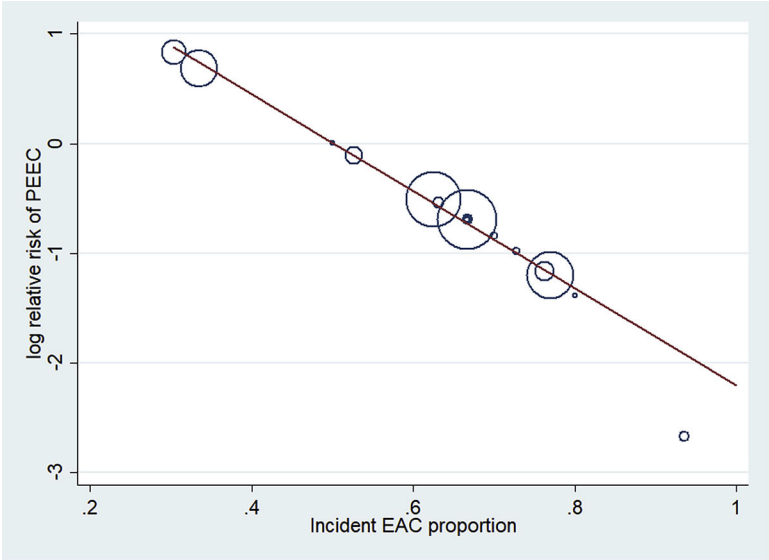

Figure 3.

Scatter plot showing the linear relationship between the relative risk of postendoscopy esophageal adenocarcinoma (PEEC) and incident esophageal adenocarcinoma (EAC).

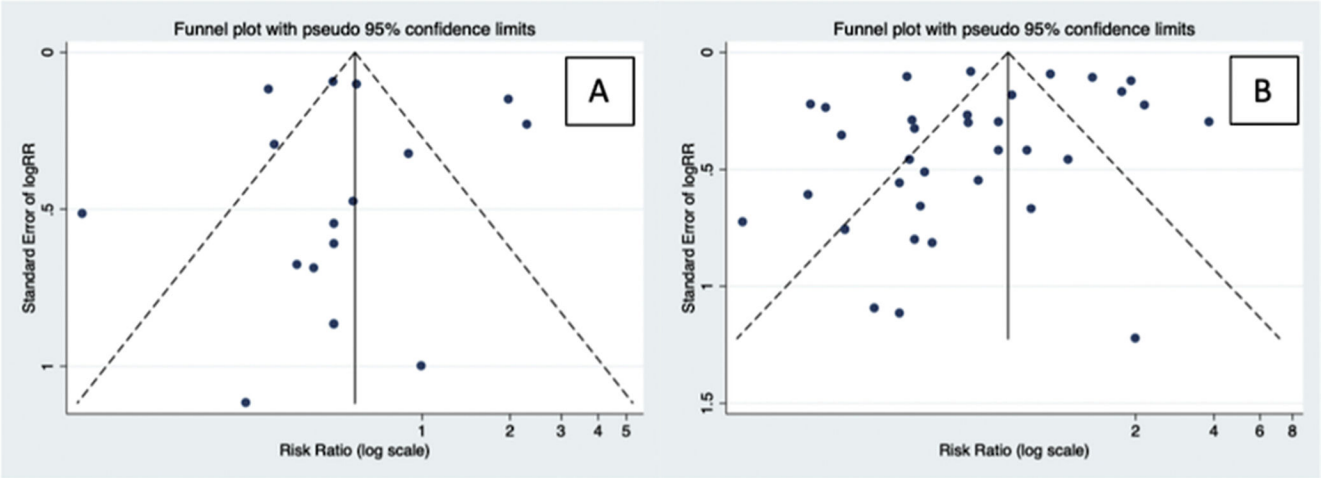

Figure 4.

Funnel plot assessing publication bias among (*A*) postendoscopy esophageal adenocarcinoma (PEEC) and (*B*) PEEC with high-grade dysplasia. RR, relative risk.

Table 1.

Study and Patient Characteristics of the 52 Included Studies

Study	Year	Baseline pathology	Country	Study setting	Publications status	Mean or median follow-up time, *y*	Mean or median age, *y*	Male, %	Total number of patients with NDBE, LGD, and IND	Long-segment BE, %	Study period
Spechler et al[13]	1984	NDBE and LGD	United States	SC	Full	3.3	NR	NR	107	NR	1962–1983
Hameeteman et al[1]	1989	NDBE and LGD	The Netherlands	SC	Full	5.2	59.3	58	49	100	–
Miros et al[15]	1991	NDBE and LGD	Australia	SC	Full	3.6	NR	NR	81	100	1981–1988
Williamson et al[16]	1991	NDBE and LGD	United States	SC	Full	3	56	63	176	100	1973–1989
Katz et al[17]	1998	NDBE and LGD	United States	SC	Full	4.8	63	82.4	102	100	1970–1994
Teodori et al[18]	1998	NDBE only	Italy	SC	Full	11.7	53	60	30	NR	1985
Bani-Hani et al[19]	2000	NDBE only	United Kingdom	SC	Full	3.6	60.9	58	357	95.5	–
Macdonald et al[20]	2000	NDBE only	United Kingdom	SC	Full	4.4	57	60.1	143	100	1984–1994
Reid et al[21]	2000	NDBE and LGD	United States	SC	Full	3.9	62	81	327	100	1983–1998
Eckardt et al[22]	2001	NDBE only	Germany	SC	Full	10	61	58.3	60	100	1980–1994
Spechler et al[23]	2001	NDBE and LGD	United States	SC	Full	9.6	NR	NR	108	100	1997–1999
Conio et al[24]	2003	NDBE and LGD	Italy	MC	Full	5.5	59.9	81.3	166	64.5	1987–1997
Parrilla et al[25]	2003	NDBE and LGD	Spain	SC	Full	6	50	76.7	43	NR	1982–2000
Dulai et al[26]	2005	NDBE and LGD	United States	MC	Full	4.8	60	99	575	NR	1988–2002
Murphy et al[27]	2005	NDBE and LGD	Ireland	SC	Full	3.4	57	71.3	178	81.5	1986–2004
Gladman et al[28]	2006	NDBE only	United Kingdom	SC	Full	5.5	62.9	55.4	195	NR	1987–2003
Vieth et al[29]	2006	NDBE only	Germany	SC	Full	6.5	60.9	67.8	748	56.1	1990–1995
Martinek et al[30]	2008	NDBE and LGD	Czech Republic	SC	Full	5.2	59.4	75.6	135	36.3	≤2006
Rossi et al[31]	2009	NDBE and LGD	Italy	SC	Full	3	63	76.2	21	52.4	1995–2005
De Jonge et al[32]	2010	NDBE and LGD	The Netherlands	PB	Full	4.8	62.1	62.5	42,207	NR	1991–2006
Vogt et al[33]	2010	NDBE and LGD	Switzerland	SC	Full	3.7	61	NR	82	NR	–
Bhat et al[34]	2011	NDBE and LGD	Ireland	PB	Full	7	NR	57.9	8711	58.2	1993–2005
Den Hoed et al[35]	2011	NDBE and LGD	The Netherlands	PB	Full	14.9	62.4	54.9	133	100	1973–1986

Study	Year	Baseline pathology	Country	Study setting	Publications status	Mean or median follow-up time, *y*	Mean or median age, *y*	Male, %	Total number of patients with NDBE, LGD, and IND	Long-segment BE, %	Study period
Hvid-Jensen et al[36]	2011	NDBE and LGD	Denmark	PB	Full	5.2	62.7	66.8	11,028	NR	1992–2009
Younes et al[37]	2011	NDBE, LGD, and IND	United States	SC	Full	3.4	NR	NR	276	NR	–
Rugge et al[38]	2012	NDBE, LGD, and IND	Italy	MC	Full	3.7	60	76.8	847	42	<2003
Choi et al[39]	2015	IND only	United States	SC	Full	1.2	63	78.1	96	31.2	2005–2013
Melson et al[42]	2015	NDBE only	United States	SC	Full	At least 3 years	NR	NR	184	0	2003–2011
Horvath et al[40]	2015	IND only	United States	SC	Full	4.9	63	74.1	107	<50	1992–2007
Kestens et al[41]	2015	IND only	The Netherlands	PB	Full	3	60.9	69.6	842	NR	2002–2011
Picardo et al[43]	2015	NDBE, LGD, and IND	Northern Ireland	SC	Full	4.2	59	67.1	1045	33.7	≤2012
Visrodia et al[45]	2016	NDBE, LGD, and IND	United States	PB	Full	4.8	61	69.5	210	55	1976–2011
Royston et al[44]	2016	NDBE and LGD	United Kingdom	SC	Full	7.5	NR	55.1	1468	NR	1977–2011
Holmberg et al[46]	2017	NDBE and LGD	Sweden	PB	Full	2.3	66	67.6	7932	NR	2006–2013
Krishnamoorthi et al[48]	2017	NDBE only	United States	MC	Full	3.8	63	78.1	485	NR	1998-NR
Krishnamoorthi et al[47]	2017	LGD only	United States	MC	Full	4.8	63.2	NR	300	>84.1	1998-NR
Nguyen et al[49]	2017	NDBE and LGD	United States	PB	Full	4.9	62	100	28,561	NR	2004–2009
Lee et al[51]	2018	NDBE only	Taiwan	SC	Full	3.7	64.4	78.4	51	22	2008–2017
Van Putten et al[53]	2018	NDBE and LGD	Ireland	PB	Full	NR	60.8	58.3	13,159	16.9	1993–2010
Parasa et al[52]	2018	NDBE and LGD	United States, The Netherlands	MC	Full	5.9	55.4	84	2697	>50	1985–2014
Jankowski et al[50]	2018	NDBE and LGD	United Kingdom, Canada	MC	Full	8.9	NR	79	2557	52.2	2005–2009
Peters et al[55]	2019	NDBE only	The Netherlands	PB	Full	4.4	57.9	68.1	12,728	50	2003–2013
Alnasser et al[54]	2019	NDBE and LGD	Canada	SC	Full	5	NR	71.8	518	18.9	2000–2010
Dasari et al[56]	2019	LGD only	United States	MC	Abstract only	6.2	62.3	87.2	369	>50	–
Hoefnagel et al[57]	2019	NDBE only	The Netherlands	MC	Abstract only	7.25	60	80.5	334	<50	–
Thota et al[58]	2019	NDBE only	United States	SC	Abstract only	4.6	59.8	74.1	1020	50	–

Study	Year	Baseline pathology	Country	Study setting	Publications status	Mean or median follow-up time, *y*	Mean or median age, *y*	Male, %	Total number of patients with NDBE, LGD, and IND	Long-segment BE, %	Study period
Kambhampati et al[59]	2020	NDBE and LGD	United States	SC	Full	7.8	68.5	77.8	460	36.5	1992–2013
O'Byrne et al[61]	2020	NDBE, LGD, and IND	Ireland	MC	Full	2.7	60	68.8	2244	58	2008–2020
Pouw et al[62]	2020	LGD only	Europe	MC	Full	6	NR	NR	68	NR	2013–2017
Song et al[64]	2020	LGD only	United States	SC	Full	3.75	65.2	100	69	52.3	2006–2016
Peleg et al[63]	2020	NDBE and LGD	Israel	SC	Abstract only	3.7	62.3	74.4	324	NR	–
Dhaliwal et al[60]	2021	NDBE and LGD	United States	PB	Full	NR	63.2	75.3	1013	>50	1991–2019

BE, Barrett's esophagus; IND, indefinite for dysplasia; LGD, low-grade dysplasia; MC, multicenter; NDBE, nondysplastic Barrett's esophagus; NR, not reported; PB, population based; SC, single center.

Table 2.

Pooled Proportion of PEEC and PEEC+HGD Among Included Studies Categorized Based on Primary and Secondary Outcomes

	EAC only			EAC+HGD		
		PEEC	Incident EAC		PEEC with HGD	Incident EAC and HGD
	Studies, n	Pooled weighted proportion, % (95% CI)	Pooled weighted proportion, % (95% CI)	Studies, n	Pooled weighted proportion, % (95% CI)	Pooled weighted proportion, % (95% CI)
Overall	32	21 (13%–31%)	79 (69%–87%)	42	26 (19%–34%)	74 (66%–81%)
Baseline pathology						
NDBE only	8	17 (11%–23%)	83 (77%–89%)	10	14 (8%–19%)	86 (81%–92%)
LGD only	1	–	–	4	44 (17%–74%)	56 (26%–83%)
IND only	1	–	–	3	39 (25%–54%)	61 (46%–75%)
NDBE and LGD	19	19 (8%–32%)	81 (68%–92%)	20	25 (14%–36%)	75 (64%–86%)
Follow-up time						
≥5 y	13	10 (0%–32%)	90 (68%–100%)	16	19 (7%–35%)	81 (65%–93%)
<5 y	19	28 (19%–39%)	72 (61%–81%)	24	31 (22%–40%)	69 (60%–78%)
Region						
North America	10	15 (2%–33%)	85 (67%–98%)	15	26 (14%–40%)	74 (60%–86%)
Europe	20	25(15%–37%)	75 (63%–85%)	24	29 (21%–38%)	71 (62%–79%)
Biopsy protocol						
Seattle protocol	8	29 (15%–45%)	71 (55%–85%)	11	33 (17%–51%)	67 (49%–83%)
Non-Seattle protocol	24	20 (11%–31%)	80 (69%–89%)	31	24 (16%–32%)	76 (68%–84%)
Publication year						
2000 and before	9	5 (0%–19%)	95 (81%–100%)	5	0 (0%–15%)	100 (34%–100%)
2001–2005	6	3 (0%–21%)	97 (79%–100%)	3	13 (0%–50%)	87 (50%–100%)
2006–2010	5	30 (25%–35%)	70 (65%–75%)	6	29 (25%–33%)	71 (67%–75%)
2011–2015	4	46 (21%–72%)	54 (28%–79%)	9	41 (29%–53%)	59 (47%–71%)
2016–2020	8	30 (16%–46%)	70 (54%–87%)	19	26 (19%–34%)	74 (64%–84%)

CI, confidence interval; EAC, esophageal adenocarcinoma; IND, indefinite for dysplasia; HGD, high-grade dysplasia; LGD, low-grade dysplasia; NDBE, non-dysplastic Barrett's esophagus; PEEC, postendoscopy esophageal adenocarcinoma.