Incidence of esophageal adenocarcinoma in Barrett's esophagus with low-grade dysplasia: a systematic review and meta-analysis CME

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Background: The natural history of low-grade dysplasia (LGD) in patients with Barrett's esophagus (BE) is unclear.

Objective: We performed a systematic review and meta-analysis of studies that reported the incidence of esophageal adenocarcinoma (EAC) and/or high-grade dysplasia (HGD) among patients with BE with LGD.

Design: Systematic review and meta-analysis of cohort studies.

Patients: Patients with BE-LGD, with mean cohort follow-up $\geq$2 years.

Main Outcome Measurements: Pooled incidence rates with 95% confidence intervals (CI) of EAC and/or BE-HGD.

Results: We identified 24 studies reporting on 2694 patients with BE-LGD, with 119 cases of EAC. Pooled annual incidence rates of EAC alone and EAC and/or HGD in patients with BE-LGD were 0.54% (95% CI, 0.32-0.76; 24 studies) and 1.73% (95% CI, 0.99-2.47; 17 studies). The results were stable across study setting and location and in high-quality studies. Substantial heterogeneity was observed, which could be explained by stratifying based on LGD/BE ratio as a surrogate for quality of pathology; the pooled annual incidence rates of EAC were 0.76% (95% CI, 0.44-1.09; 14 studies) for LGD/BE ratio $<$0.15 and 0.32% (95% CI, 0.07-0.58; 10 studies) for LGD/BE ratio $>$0.15. The annual rate of mortality not related to esophageal disease in patients with BE-LGD was 4.7% (95% CI, 3.2-6.2; 4 studies).

Limitations: Substantial heterogeneity was observed in the overall analysis.

Conclusion: The incidence of EAC among patients with BE-LGD is 0.54% annually. The LGD/BE ratio appears to explain the variation observed in the reported incidence of EAC in different cohorts. Conditions not related to esophageal disease are a major cause of mortality in patients with BE-LGD, although additional studies are warranted. (Gastrointest Endosc 2014;79:897-909.)

Abbreviations: BE, Barrett's esophagus; EAC, esophageal adenocarcinoma; HGD, high-grade dysplasia; IR, incidence rate; LGD, low-grade dysplasia.

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Barrett's esophagus (BE) is a well-identified precursor for esophageal adenocarcinoma (EAC).[1] The risk of EAC in patients with BE is highly variable, and presence and grade of dysplasia are key predictors of risk of progression to EAC. Although the estimated annual risk of EAC in patients with nondysplastic BE is 1 in 300 patients,[2] the corresponding risk in patients with BE with high-grade dysplasia (HGD) is 1 in 15 patients.[3] The risk of progression to EAC in patients with BE with low-grade dysplasia (LGD) is poorly estimated, with annual incidence rates ranging from <0.2% to more than 3% annually in large studies alone.[4,5] A previous meta-analysis of 16 studies (including surgical series) had estimated the annual incidence rate of EAC in patients with BE-LGD to be 1.6%, with considerable heterogeneity.[6] However, since then, several large, population-based studies have been published, with reported lower incidence of EAC in these patients.[7,8] It is important to accurately estimate the incidence of EAC as well as causes of mortality in patients with BE-LGD to decide on appropriate treatment and surveillance strategy.

One of the reasons for wide variability in the reported risk of EAC in patients with BE-LGD is significant interobserver variability in the diagnosis of LGD among pathologists, with most cases of LGD being mistaken for nondysplastic or "indefinite for dysplasia" BE, especially in the presence of esophageal inflammation.[9] Hence, it is likely that in for studies in which the diagnosis of LGD was made liberally (ie, a high proportion of patients in the cohort were diagnosed with BE-LGD), observed EAC incidence would be low (because several patients with nondysplastic BE with its associated low risk of progression to EAC may have been misclassified as having BE-LGD). In contrast, for studies in which a stringent diagnosis of BE-LGD is made, the estimated risk of progression to EAC may be higher. One surrogate of the presence of selection bias and quality of pathology may be estimating a ratio of LGD to BE (LGD/BE), that is, the proportion of patients with LGD in the entire BE cohort. Population-based studies estimate a prevalence rate of BE-LGD of approximately 13% to 15%.[10,11]

Hence, to better understand the risk of EAC and/or HGD in patients with BE-LGD as well as to estimate the rate of mortality from conditions not related to esophageal disease in these patients, we performed a systematic review and meta-analysis of cohort studies addressing this question. Moreover, we also estimated differences in the risk of EAC based on LGD/BE ratio and identified BE-related factors associated with risk of progression to EAC, reported in the literature.

Take-home Message

- The annual incidence of esophageal adenocarcinoma (EAC) and EAC and/or high-grade dysplasia in patients with Barrett's esophagus/low-grade dysplasia (BE-LGD) is 0.54% and 1.73%, respectively. The risk of progression to EAC is dependent on the LGD/BE ratio (proportion of patients with LGD in the entire BE cohort); the estimated rate is 0.76% if the ratio is <0.15 and 0.32% if the ratio is >0.15. This may serve as a surrogate for quality of pathology.
- The annual rate of mortality from causes not related to esophageal disease is high (4.7%) in patients with BE-LGD. Surveillance strategies in patients with BE-LGD may need to be reconsidered, especially in light of high causes of mortality not related to esophageal disease.

METHODS

Search strategy

We conducted a systematic literature search of MEDLINE (1966 to December 31, 2012) and EMBASE (1988 to December 31, 2012) for all relevant articles on the risk of EAC in patients with BE. Key words used in the search included a combination of "Barrett's esophagus," "Barrett's neoplasia," "Barrett's epithelium," or "intestinal metaplasia" and "esophageal cancer," "esophageal adenocarcinoma," or "esophageal neoplasia." The search was restricted to the studies in human participants published in the English language in peer-reviewed journals. Two authors (A.V.A. and T.K.D.) independently reviewed the title and abstract of studies identified in the primary search, to exclude studies that did not address the research question of interest, based on prespecified inclusion and exclusion criteria (details later). The full text of the remaining articles was examined to determine whether it contained relevant information. Any discrepancy in article selection was resolved by consensus, and in discussion with a coauthor (S.S.). Next, the bibliographies of the selected articles as well as systematic and narrative review articles on the topic were manually searched for additional articles. Conference proceedings, which did not undergo peer review, were excluded from our analysis. In case of missing information, attempts were made to contact the authors with specific questions regarding their studies.

Study selection

In this meta-analysis, we included cohort studies that met the following specific criteria: (1) specified number of patients with biopsy-proven BE-LGD; (2) reported mean follow-up of a minimum of 2 years after the diagnosis of BE-LGD; and (3) specified number of patients with BE-LGD who developed EAC and/or HGD, along with the total person-years of follow-up for the subset of patients with BE-LGD or the mean/median follow-up of the BE-LGD or the entire BE cohort. Only cases of EAC and/or HGD that occurred >6 months after diagnosis were included. We excluded the following: (1) case-control studies, cross-sectional studies, and case series; (2) studies with a minimum follow-up of <2 years; and (3) studies that provided insufficient data to allow estimation of the incidence rate (IR) of EAC and/or HGD. We also excluded surgical series

(ie, studies on cohorts of patients who had undergone anti-reflux surgery) as well as series in patients who underwent endoscopic ablative therapy, because these represent a highly selected cohort of patients, but we included them in a sensitivity analysis. In case of multiple publications from the same cohort, data from the most recent comprehensive report were included.

Data abstraction and quality assessment

Data on study-related and BE-related characteristics as well as reported outcomes in the individual studies were abstracted onto a standardized form by at least 2 authors independently (P.M., S.S., T.K.D.). Details of data abstraction are reported in the supplemental appendix (Appendix available online at www.giejournal.org).

The quality of included studies was assessed by using a scale modified from the Newcastle-Ottawa scale for cohort studies.[12] This quality score consisted of 7 questions: representative of the average adult in the community (1 point for population-based studies, 0.5 point for multicenter studies; 0 point for a single-center hospital-based study); large cohort size (1 point if cohort size >200 patients with BE, 0.5 point if cohort size between 100 and 200 patients, 0 point if cohort size <100 patients with BE); definite histologic confirmation of BE (1 point if confirmed by consensus of 2 expert pathologists; 0.5 point if reviewed by 1 expert GI pathologist; 0 point if reviewed only by community pathologist or not reported in study); adequate follow-up of cohort for outcome to occur (1 point if mean follow-up of entire cohort >5 years, 0.5 point if cohort follow-up between 3 and 5 years, 0 point if mean follow-up of cohort <3 years); clear information on duration of follow-up of patients with BE-LGD (1 point if reported in study in total person-years, 0.5 point if reported as mean follow-up of BE-LGD cohort, 0 point if imputed from entire BE cohort); attrition rate (1 point if >80% of cohort followed-up, 0.5 point if 60%-80% cohort followed-up, 0 point if >40% lost to follow-up); definite information on progression of BE-LGD (1 point if adequate information on rate of progression from BE-LGD to BE-HGD and EAC separately, 0.5 point if only information on rate of progression to EAC, without information on BE-HGD). A score of ≥5, 3 to 4, and ≤2 was considered suggestive of high-quality, medium-quality, and low-quality study.

Outcomes assessed

The primary analysis focused on assessing the incidence of EAC in patients with BE-LGD, and a secondary analysis focused on the incidence of EAC and/or HGD in patients with BE-LGD. Additionally, to assess whether there are differences in the reported incidence of EAC in patients based on the LGD/BE ratio, we performed stratified analysis by using a prespecified cut-off BE/LGD ratio of 0.15 (because that is the prevalence of BE in population-based studies with review of all cases by an expert GI pathologist).[10]

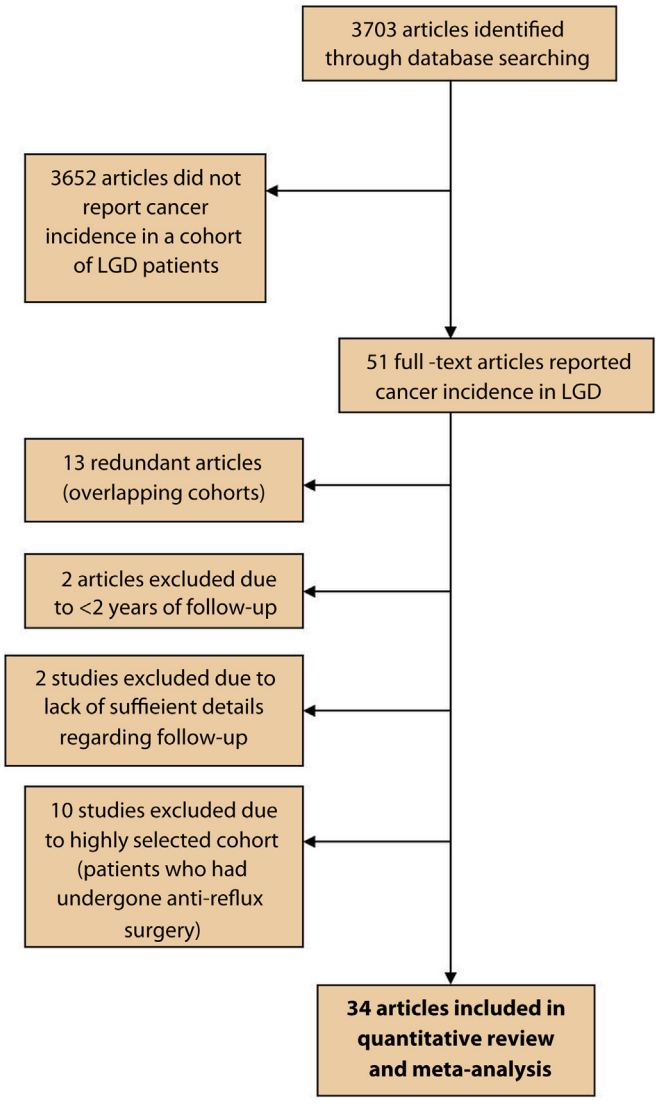

Figure 1. Study flow and selection. *LGD,* low-grade dysplasia.

A priori hypotheses to explain potential heterogeneity in the magnitude of effect among different observational studies included location of study (North America vs Europe) and study setting (population-based vs multicenter vs single-center). Sensitivity analyses based on study quality as well as after inclusion of surgical series also were performed. In addition, we performed sensitivity analysis after restricting analysis to studies in which only incident EAC was diagnosed >12 months after BE-LGD diagnosis. We also assessed differences in the incidence of EAC in prevalent versus incident LGD as well as differences based on whether a single pathologist or a consensus of pathologists established the diagnosis of LGD in studies that reported both of these estimates. We also reviewed other BE-specific factors associated with progression of BE-LGD to EAC (length of BE segment, unifocal vs multifocal LGD, one-time or persistent diagnosis of LGD), and we performed meta-analysis if feasible.

TABLE 1. Characteristics of included cohort studies, categorized based on study quality

No.	Author	Year	Country	Total no. patients w/BE	Patients w/BE-LGD	Mean follow-up, y	Total person years of follow-up for BE-LGD
High-quality studies							
1	Hvid-Jensen et al‡,[8]	2011	Denmark	11,028	621	5.2	4175* for EAC; 3835* for HGD
2	Bhat et al‡,[7]	2011	Ireland	8451	323	7.1*	2283*
3	Wani et al‡,[48]	2011	U.S.	1755	210	4.6*	960*
4	Gatenby et al‡,[49]	2009	U.K.	146	146	4*	590*
5	Dulai et al‡,[50]	2005	U.S.	575	134	4.1*	548*
6	Schouten et al§,[11]	2011	Ne.	593	97	5*	488*
7	Jung et al§,[10]	2011	U.S.	365	53	7.8	413
8	Lim et al§,[5]	2007	U.K.	357	34	11	374
9	Vieth et al‖,[51]	2006	Germany	748	19	4.5*	86*
10	Curvers et al‖,†,[52]	2010	Ne.	1198	19	3.2*	60*
11	Conio et al‡,[53]	2003	Italy	166	16	5.5	88 for EAC; 85.5 for HGD
Medium-quality studies							
12	Schnell et al‡,[4]	2001	U.S.	1099	738	7.3	5387
13	Reid et al‡,[54]	2000	U.S.	327	43	3.9	168
14	Alcedo et al‡,[55]	2009	Spain	197	32	4.3	136
15	Switzer-Taylor et al‡,[56]	2008	N.Z.	212	32	3.9	126
16	Younes et al‖,[57]	1997	U.S.	61	25	3.3	83
17	Wong et al‖,[58]	2010	U.S.	248	22	6	132
18	Miros et al‡,[59]	1991	Australia	81	20	3.6	76
19	Montgomery et al§,†,[60]	2001	U.S.	138	15	1.7*	26.3*
20	Hage et al‡,[61]	2004	Ne.	75	11	12.8	140
21	Hameeteman et al‖,[62]	1989	Ne.	50	6	5.2	31
22	Spechler et al‖,[63]	1984	U.S.	115	4	3.3	13
23	Wilkinson et al‡,[64]	1999	U.K.	23	1	5	5
Low-quality studies							
24	Ajumobi et al§,[65]	2010	U.S.	165	62	4.2	258
Surgical series (included in sensitivity analysis)							
1	Basu et al‡,[38]	2004	U.K.	138	16	1.7*	27*
2	Demeester et al‡,[39]	1990	U.S.	47	9	3	27
3	O'Riordan et al‡,[40]	2004	Ireland	57	8	3.8	30
4	Parrilla et al‡,[41]	2003	Spain	101	8	6.6	53
5	Chen et al‡,[42]	2001	Canada	45	8	4	32
6	Bowers et al‡,[43]	2002	U.S.	104	4	4.5	18
7	Low et al‡,[44]	1999	U.S.	14	4	2	8
8	Biertho et al‡,[45]	2007	Belgium	92	3	4.3	13
9	Desai et al‡,[46]	2003	U.S.	68	3	2.7	8
10	Zaninotto et al‡,[47]	2005	Italy	35	2	2.5	5

BE, Barrett's esophagus; *LGD,* low-grade dysplasia; *EAC,* esophageal adenocarcinoma; *HGD,* high-grade dysplasia; *NR,* not reported; *U.S.,* United States; *U.K,* United Kingdom; *Ne.,* Netherlands; *N.Z.,* New Zealand.
Surgical series (made up of studies on patients who had undergone anti-reflux surgery) also are shown.
Numbers rounded to near whole numbers.
Studies are arranged based on quality, and within each category, studies are arranged by cohort size of BE-LGD.
*Patient-years data provided for the actual LGD cohort.
†Included patients with expert pathologist diagnosis of LGD, as opposed to community pathologist classification.
‡Patients with incident cancers >1 year after BE-LGD diagnosis.
§Patients with incident cancers >6 mo after BE-LGD diagnosis.
‖No clear report on how incident cases were defined.

TABLE 1. Continued

No. of BE-LGD patients w/incident EAC	EAC rate (per 1000 person years)	No. of BE-LGD patients w/incident HGD	No. of incident HGD-EAC (combined)	% of BE-LGD patients in total BE population	No. of deaths not related to esophageal cause
23	4.3	43	NR	5.6	NR
21	9.2	9	30	3.8	NR
6	6.3	21	24	12	NR
8	13.5	5	13	100	NR
2	3.6	5	7	23.3	26
2	4.1	NR	NR	15.5	40
1	2.4	2	3	14.5	13
9	33.1	NR	NR	9.5	11
4	46.5	0	4	2.5	NR
2	33.3	6	8	1.6	NR
2	22.7	1	2	9.6	NR
10	1.9	NR	NR	67.2	NR
3	17.9	0	3	13.1	NR
0	0	0	0	16.2	NR
1	7.9	3	4	15.1	NR
4	48.2	1	5	41	NR
2	15.1	0	2	8.9	NR
1	13.9	0	1	24.7	NR
3	76.9	4	7	18.8	NR
1	7.1	1	2	14.7	NR
3	96.7	1	4	12	NR
0	0	0	0	3.5	NR
0	0	0	0	4.3	NR
0	0	NR	NR	37.6	NR
0	0	0	0	11.6	NR
0	0	0	0	19.1	NR
2	66.7	0	2	14	NR
1	18.9	0	1	7.9	NR
0	0	0	0	17.8	NR
0	0	0	0	3.8	NR
0	0	0	0	28.6	NR
0	0	0	0	3.3	NR
0	0	0	0	4.4	NR
0	0	0	0	5.7	NR

TABLE 2A. Quality of included studies: high-quality studies

Question	Scoring scheme	Bhat[7]	Conio[53]	Curvers[52]	Dulai[50]
Representative of the average adult in the community	1 point: population-based studies 0.5 point: multicenter studies 0 point: single-center hospital-based study	1	0.5	0.5	0.5
Large cohort size	1 point: cohort size >200 patients with BE 0.5 point: cohort size 100-200 patients 0 point: cohort size of <100 patients with BE	1	0.5	1	1
Definite histologic confirmation of BE	1 point: confirmed by consensus of 2 expert pathologists 0.5 point: reviewed by 1 expert pathologist 0 point: reviewed by community pathologist only or not reported in study	0.5	0.5	1	0.5
Adequate follow-up of cohort for outcome to occur	1 point: mean follow-up of entire cohort >5 y 0.5 point: cohort follow-up 3-5 y 0 point: mean follow-up of cohort <3 y	1	1	0.5	0.5
Clear information on duration of follow-up of patients with BE-LGD	1 point: reported in study in total person years 0.5 point: reported as mean follow-up of BE-LGD cohort 0 point: imputed from entire BE cohort	1	0.5	0.5	1
Attrition rate	1 point: >80% of cohort followed-up 0.5 point: 60%-80% of cohort followed-up 0 point: >40% lost to follow-up	1	1	1	1
Definite information on progression of BE-LGD	1 point: adequate information on rate of progression from BE-LGD to BE-HGD and EAC separately 0.5 point: only information on rate of progression to EAC, without information on BE-HGD	1	1	1	1
Total score (maximum = 7; high quality ≥5; medium quality 3-4; low quality ≤2)		4	6.5	5	5.5

BE, Barrett's esophagus; *LGD,* Low-grade dysplasia; *HGD,* high-grade dysplasia; *EAC,* esophageal adenocarcinoma.

We analyzed the rate of mortality related to causes other than esophageal disease in these studies, and we compared it to the incidence of diagnosis of EAC in this cohort of patients with BE-LGD.

Statistical analysis

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, by using a predefined protocol.[13] This study differs from many meta-analyses in the literature in that summary outcome measure was pooled IR, rather than a pooled estimate of effect size (measuring the effect of membership in one categorization of patients' experiences vis-à-vis another). We used meta-analysis techniques to calculate the pooled estimates in each case following the methods suggested by DerSimonian and Laird,[14] and our application can be seen to fit within their general approach (where effect is measured by probability or risk). When the incidence of EAC was zero in a study, a correction of 0.05 was added to the number of incident cases and person years follow-up before statistical analysis.[15] We assessed heterogeneity between study-specific estimates by using two methods.[16,17] First, the Cochran Q statistical test for heterogeneity, which tests the null hypothesis that all studies in a meta-analysis have the same underlying magnitude of effect, was done. Because this test is underpowered to detect moderate degrees of heterogeneity, a P value of $< .10$ was considered suggestive of significant heterogeneity.[18] Second, when heterogeneity was present, in order to estimate what proportion of total variances across studies was due to heterogeneity rather than chance, the I^2 statistic was calculated. In this, values of <30%, 30% to 60%, 61% to 75%, and >75% were suggestive of low, moderate, substantial, and considerable heterogeneity, respectively.[19] Once heterogeneity was noted, between-study sources of heterogeneity were investigated by using subgroup analyses by stratifying original estimates according to study characteristics as described earlier. A P value for differences between subgroups of $< .10$ was considered statistically significant. Publication bias was ascertained, qualitatively, by visual inspection of funnel plot and quantitatively, by the Egger test.[20]

All analyses were performed by using comprehensive meta-analysis software, version 2 (Biostat, Englewood, NJ).

RESULTS

From a total of 3703 citations identified by using our search strategy, 51 studies reported EAC incidence among

TABLE 2A. Continued

Gatenby[49]	Hvid-Jensen[8]	Jung[10]	Lim[5]	Schouten[11]	Vieth[51]	Wani[48]
0.5	1	1	0	1	0	0.5
1	1	1	1	1	1	1
0.5	0	0.5	1	0.5	1	1
0.5	1	1	1	1	0.5	1
1	1	0	0.5	1	1	1
0.5	1	1	1	1	1	1
1	1	1	0.5	0.5	1	1
5	6	6.5	5	6	5.5	6.5

patients with BE-LGD. Of these, 17 studies were excluded because they did not meet the study criteria (2 studies had follow-up <2 years;[21,22] 2 studies lacked precise details regarding follow-up;[23,24] there were 13 studies with redundant study populations[25-37]); an additional 10 studies on patients who had undergone anti-reflux surgery were excluded from the primary analysis but were included in a sensitivity analysis.[38-47] Twenty-four studies were included in the final analyses.[4,5,7,8,10,11,48-65] The schematic diagram of study selection is illustrated in Figure 1.

Characteristics and quality of included studies

Table 1 describes the characteristics of the included studies, and Table 2 describes the quality of the included studies. Of 24 studies, 17 reported sufficient data to estimate the incidence of EAC and/or HGD. Five studies were population-based, and 6 studies were multicenter studies. The majority of studies were performed in Europe (15 studies), and the remaining were performed in the United States; none of the studies were performed on the Asian population. Fourteen study cohorts comprised of >200 patients with BE and 11 other studies reported a mean cohort follow-up of >5 years. Thirteen studies reported precise data for estimation of follow-up of patients with BE-LGD; for 11 studies, the person years of follow-up was imputed from mean and/or median follow-up of the entire BE cohort. Most of the studies (20/24) had complete follow-up, with a <20% attrition rate. Overall, 11 of 24 studies were considered high quality, and 12 studies were considered medium quality; 1 study was deemed low quality. The LGD/BE ratio ranged from 1.6% to 67.2%; 1 study was made up only of patients with BE-LGD.

Incidence of esophageal adenocarcinoma

On meta-analysis of 24 independent cohort studies (2694 patients with BE-LGD, 16,672 patient years of follow-up, 119 cases of EAC), the pooled IR of EAC was 0.54/100 patient years of follow-up (or 0.54% annually) (95% confidence interval [CI], 0.32%-0.76%), with rates in individual studies ranging from 0.02% to 11.43% (Fig. 2). Substantial heterogeneity was observed in the overall analysis (I^2 = 63%). The pooled annual IR of the combined outcome of EAC and/or BE-HGD was 1.73% (95% CI, 0.99%-2.47%) based on 17 studies that reported both EAC and BE-HGD as outcome, with considerable heterogeneity (I^2 = 78%), with rates varying from 0.04% to 26.67% (Fig. 3).

Subgroup analysis

When we stratified studies based on the LGD/BE ratio by using 0.15 as a cut-off, we observed that studies with

TABLE 2B. Quality of included studies: medium and low-quality studies

Question	Scoring scheme	Alcedo[55]	Hage[61]	Hemeeteman[62]	Miros[59]
Representative of the average adult in the community	1 point: population-based studies, 0.5 point: multicenter studies 0 point: single-center hospital-based study	1	0	0	0
Large cohort size	1 point: cohort size >200 patients with BE 0.5 point: cohort size 100-200 patients 0 point: cohort size <100 patients with BE	0	0.5	0	0
Definite histologic confirmation of BE	1 point: confirmed by consensus of 2 expert pathologists 0.5 point: reviewed by 1 expert pathologist 0 point: reviewed by community pathologist only or not reported in study	0.5	0.5	0.5	0.5
Adequate follow-up of cohort for outcome to occur	1 point: mean follow-up of entire cohort >5 years 0.5 point: cohort follow-up 3-5 years 0 point: mean follow-up of cohort <3 years	0.5	1	1	0.5
Clear information on duration of follow-up of patients with BE-LGD	1 point: reported in study in total person years 0.5 point: reported as mean follow-up of BE-LGD cohort 0 point: imputed from entire BE cohort	0	0	0.5	1
Attrition rate	1 point: >80% of cohort followed-up 0.5 point: 60%-80% cohort followed-up 0 point: >40% lost to follow-up	1	1	1	0.5
Definite information on progression of BE-LGD	1 point: adequate information on rate of progression from BE-LGD to BE-HGD and EAC separately 0.5 point: only information on rate of progression to EAC, without information on BE-HGD	1	1	1	1
Total score (maximum = 7; high quality ≥5; medium quality 3-4; low quality ≤2)		4	4	4	3.5

BE, Barrett's esophagus; *LGD,* low-grade dysplasia; *HGD,* high-grade dysplasia; *EAC,* esophageal adenocarcinoma.

a high LGD/BE ratio (>0.15) reported a lower incidence of EAC (IR, 0.32%; 95% CI, 0.07%-0.58%; 10 studies), whereas studies with low LGD/BE ratios (<0.15) reported a higher incidence of EAC (IR, 0.76%; 95% CI, 0.45%-1.07%; 14 studies) ($P_{interaction}$ = .03). Moreover, the observed heterogeneity in studies with low LGD/BE ratios was low (I^2 = 35%). Otherwise, the estimated annual incidence of EAC was stable in studies performed in North America (IR, 0.40%; 95% CI, 0.03%-0.78%; 9 studies) and Europe (IR, 0.63%; 95% CI, 0.36%-0.90%; 15 studies), with no significant difference between groups ($P_{interaction}$ = .34). The estimated EAC risk also was stable across population-based studies (IR, 0.44%; 95% CI, 0.13%-0.74%; 5 studies), multicenter studies (IR, 0.79%; 95% CI, 0.23%-1.36%; 6 studies), and single-center studies (IR, 0.63%; 95% CI, 0.21%-1.05%; 13 studies) ($P_{interaction}$ =0.49).

Three studies reported the IR of EAC and/or HGD in patients with prevalent and incident BE-LGD,[7,8,48] and on meta-analysis of these studies, there was no significant difference in the incidence of EAC and/or HGD in patients with incident BE-LGD (IR, 1.31%; 95% CI, 0.47%-2.16%) compared with prevalent BE-LGD (IR, 1.24%; 95% CI, 0.36%-2.12%) ($P_{interaction}$ = .91). Data were not sufficient to allow comparison of rate of EAC alone.

In 4 studies, the biopsy specimens of patients initially classified as BE-LGD by individual pathologists were re-reviewed by expert GI pathologists, and a consensus diagnosis of BE-LGD was reached in a subset of patients.[5,48,52,60] In 2 studies with patients initially classified as BE-LGD by community pathologists, there was considerable discrepancy after consensus diagnosis by expert pathologists (initially diagnosed with BE-LGD—171; number of patients with BE-LGD after consensus of pathologists—37; 21.6% agreement) and the subsequent reported incidence estimate of EAC[52,60]; in 2 other studies from referral centers, there was relatively greater agreement of consensus diagnosis of BE-LGD with the initial diagnosis (initially diagnosed with BE-LGD—122; number of patients with BE-LGD after consensus of pathologists—55; 45.1% agreement), and the overall IR of EAC was not significantly different.[5,48] Overall, a numerical difference (although not statistically significant) in the IR of EAC and/or HGD was observed between patients initially classified as having BE-LGD by a single pathologist (IR, 2.15%; 95% CI, 0.54%-3.75%) and those having a consensus expert diagnosis of BE-LGD (IR, 5.70%; 95% CI, 0.33%-11.08%) ($P_{interaction}$ = .21). Data were not sufficient to allow comparison of rate of EAC alone.

TABLE 2B. Continued

Montgomery[60]	Reid[54]	Schnell[4]	Spechler[63]	Switzer-Taylor[56]	Wilkinson[64]	Wong[58]	Younnes[57]	Ajumobi[65]
0.5	0	0	0	0	0	0	0	0
0.5	1	1	0.5	1	0	1	0	0.5
1	0.5	0.5	0.5	1	0.5	0.5	0.5	0.5
0	0.5	1	0.5	0.5	1	0.5	0.5	0.5
0.5	0	0	0	0	0	0	0	0
0	1	1	1	1	1	1	1	0
1	0.5	0.5	0.5	1	1	1	1	0.5
3.5	3.5	4	3	4.5	3.5	4	3	2

Besides these, only 1 study reported the IR of EAC in patients with unifocal or multifocal BE-LGD and observed a statistically insignificant difference in the incidence of EAC (unifocal BE-LGD vs multifocal BE-LGD: IR, 0.27% vs 1.89%; $P = .08$).[48] The same study also reported a numerically higher but statistically nonsignificant incidence of EAC in patients with long-segment (>3 cm) BE-LGD (IR 0.60%), as compared with patients with short-segment (<3 cm) BE-LGD (IR 0.29%) ($P = .39$).

Sensitivity analysis and publication bias

On restricting analysis to 11 high-quality studies,[5,7,8,10,11,48-53] the pooled IR of EAC was 0.67% (95% CI, 0.40%-0.94%), with moderate heterogeneity ($I^2 = 48\%$). The pooled estimate of EAC, based on 12 medium-quality studies,[4,54-64] was 0.46% (95% CI, 0.07%-0.85%), with moderate heterogeneity ($I^2 = 35\%$). On specifically limiting analysis to 6 studies in which two expert GI pathologists made the diagnosis of BE-LGD, the pooled annual IR of EAC was 1.6% (95% CI, 0.38%-2.83%). On including 10 studies that included patients who had undergone anti-reflux surgery, the pooled IR of EAC was 0.51% (95% CI, 0.31%-0.71%), and the pooled IR of EAC and/or BE-HGD was 1.38% (0.78%-1.98%), with moderate heterogeneity in the analysis ($I^2 = 49\%$ and 67%, respectively). The overall incidence of EAC in the subset of studies on patients who had undergone anti-reflux surgery for any indication was 0.34% (95% CI, 0.00%-1.10%), with low heterogeneity in the analysis ($I^2 = 0\%$).[38-47] On restricting analysis to 13 studies in which only incident EAC was diagnosed >12 months after the BE-LGD diagnosis, the results were not significantly different (IR, 0.53%; 95% CI, 0.33%-0.73%). To assess whether any one study had a dominant effect on the meta-analysis IR, we also excluded each study at a time and analyzed its effect on the main summary estimate and Cochran Q test P value for heterogeneity. On this analysis, the overall annual IR of EAC ranged from 0.48% to 0.61%, with no single study significantly affecting heterogeneity. Subsequently, we excluded 2 outlier studies with extremely low IRs of EAC (Ajumobi et al,[65] with IR of 0.02% and Alcedo et al,[55] with IR of 0.04%) and 2 studies with extremely high IRs of EAC (Montgomery et al,[60] with IR of 11.43% and Hameeteman et al,[62] with IR of 9.68%) and reanalyzed the IR. The results were stable (IR of EAC, 0.63%; 95% CI, 0.42%-83%), and only moderate heterogeneity was observed in the analysis ($I^2 = 36\%$). In order to evaluate for temporal changes in reported progression rate to EAC in patients with

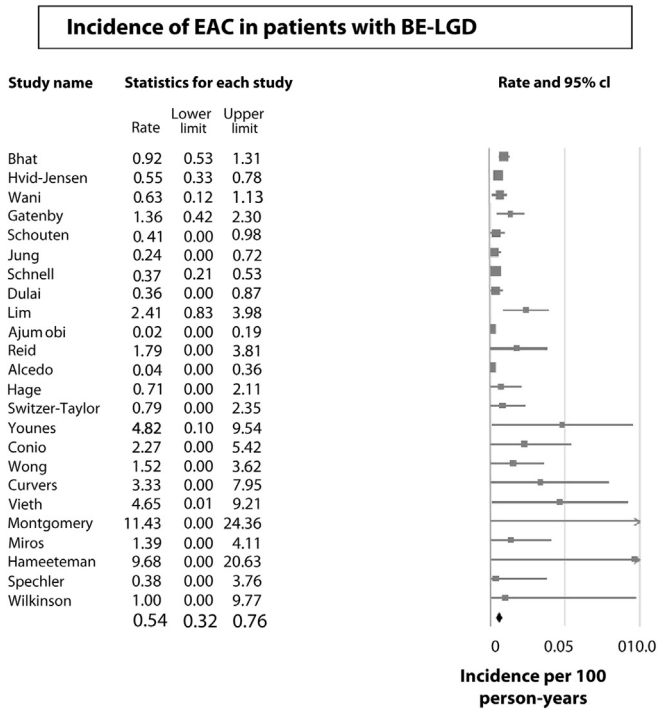

Figure 2. Incidence of esophageal adenocarcinoma in patients with Barrett's esophagus with low-grade dysplasia. *EAC,* esophageal adenocarcinoma; *BE,* Barrett's esophagus; *LGD,* low-grade dysplasia; *CI,* confidence interval.

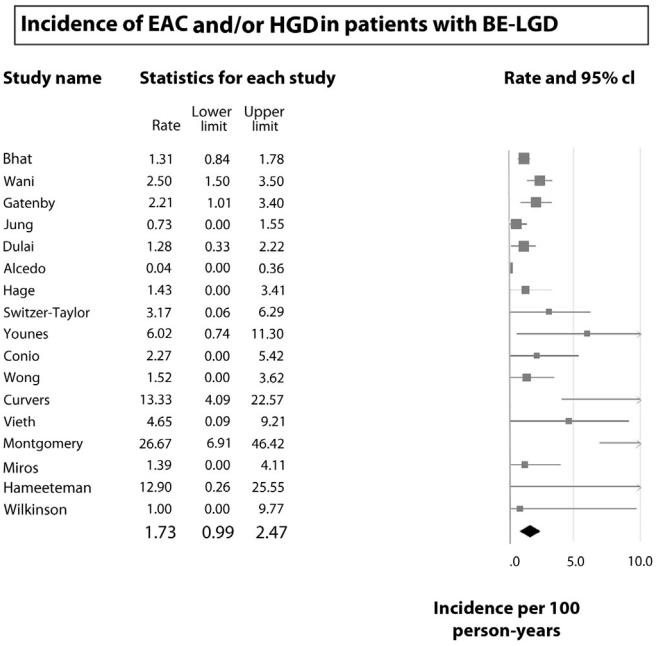

Figure 3. Incidence of esophageal adenocarcinoma and/or high-grade dysplasia in patients with Barrett's esophagus with low-grade dysplasia. *EAC,* esophageal adenocarcinoma; *HGD,* high-grade dysplasia; *BE,* Barrett's esophagus; *LGD,* low-grade dysplasia; *CI,* confidence interval.

BE-LGD, we performed a time-trend meta-analysis and observed a slight decrease in the incidence of EAC over the last decade, although this was not statistically significant (Supplementary Fig. 1, available online at www.giejournal.org).

Based on visual inspection of the funnel plot (Supplementary Fig. 2, available online at www.giejournal.org) as well as on quantitative measurement that used the Egger regression test, there was evidence of publication bias ($P < .01$). By using the trim-and-fill method, which conservatively imputes hypothetical negative unpublished studies to mirror the positive studies that cause funnel plot asymmetry,[66] we estimated the IR of EAC (after imputing the EAC rate for 11 hypothetical studies) to be 0.38% (95% CI, 0.14%-0.63%).

Incidence of mortality from conditions not related to esophageal disease

Four studies reporting on 318 patients reported cause-specific mortality in patients with BE-LGD.[5,10,11,50] In these studies, 14 patients (4.4%) developed EAC (of which 1%-2.2% died because of the cancer), whereas 90 died because of causes other than esophageal disease (28.3%). The pooled all-cause mortality rate from conditions other than esophageal disease was estimated to be 4.7% annually (95% CI, 3.2%-6.2%), with moderate heterogeneity in the analysis ($I^2 = 54.5\%$) (Supplementary Fig. 3, available online at www.giejournal.org).

DISCUSSION

Current management strategies for BE-LGD are unclear, and endoscopic eradication therapy is not routinely recommended.[1] This is because of relative paucity of data on the natural history of BE-LGD with regard to progression to EAC and/or HGD. Additionally, there are limited data on cause-specific mortality in patients with BE-LGD from which to project cost-effectiveness of surveillance and endoscopic eradication therapy in this cohort of patients. In this systematic review and meta-analysis of 24 studies in about 2700 patients with BE-LGD, we estimated that the annual incidence of progression to EAC is 0.54% (1 in 185 patients), and the rate of progression to a combined end-point of EAC and/or HGD is 1.73% annually (1 in 58 patients), albeit with substantial heterogeneity across studies. The incidence rate of progression to EAC is dependent on the prevalence of LGD in a cohort of patients with BE. For studies in which a high proportion of patients with BE are diagnosed with LGD (LGD/BE ratio >0.15), the incidence of EAC is lower (about 0.32% or 1 in 312 patients), whereas for studies in which a smaller proportion of patients are diagnosed with BE-LGD (LGD/BE ratio <0.15), the observed incidence of EAC is higher (about 0.76% or 1 in 132 patients). In studies examining cause-specific mortality in patients with BE-LGD, mortality from causes other than esophageal disease (annual incidence 4.7%) appears to be considerably higher than mortality from (or even the incidence of) EAC. Our estimate of EAC in patients with BE-LGD is significantly lower

than that previously reported in a systematic review published in 2009, in which the annual estimate of EAC was 1.6%.[6] Since the publication of that review, several additional studies including population-based cohorts on unselected patients have been published. Moreover, we excluded surgical series from the primary analysis because of a lower observed risk of progression to EAC in this highly selective cohort. We also excluded several redundant studies that had been included in the previous review.

The strengths of this review include: (1) systematic literature search with well-defined inclusion criteria carefully excluding redundant studies; (2) exclusion of surgical series in the primary analysis to minimize selection bias to allow best estimation of the natural history of BE-LGD (although addition of these studies in a sensitivity analysis did not modify the results significantly); (3) estimation of outcomes of both EAC alone as well as a combined outcome of incident EAC and/or HGD; (4) rigorous evaluation of study quality; (5) subgroup analyses to evaluate the stability of findings and identify potential factors responsible for inconsistencies; (6) identification of the LGD/BE ratio as a surrogate for selection bias and quality of pathology, being responsible for observed heterogeneity in the literature; and (7) estimating cause-specific mortality in patients with BE-LGD.

There also were several limitations, both with regard to individual studies as well as the pooled analysis. First, the included studies reported wide variability in the prevalence of LGD in a cohort of BE patients as well as potential misclassification bias because of interobserver variability in the diagnosis of BE-LGD. We observed significant differences in the incidence of EAC for studies in which the prevalence of LGD was <15% of the entire BE cohort, as compared with studies in which there was a higher diagnostic prevalence of BE-LGD. There is considerable variability in the diagnosis of BE-LGD among pathologists, particularly community pathologists and expert GI pathologists. Only 6 studies reported confirmation of BE-LGD diagnosis by expert pathologists, and these studies observed a higher rate of progression to EAC. When we performed a subgroup analysis of 4 studies, which reported EAC and/or HGD risk based on whether diagnosis was made by a single pathologist and after confirmation of BE-LGD by expert consensus of pathologists, the former generally observed a lower incidence (2.15%) as compared with the latter (5.7%). Second, studies did not consistently report the frequency of endoscopic surveillance and numbers of biopsy specimens taken at endoscopy and whether potentially chemopreventive pharmacologic interventions (such as aspirin, statins, or proton pump inhibitors) were used in the cohort.[21,67-69] Third, there was variability in study quality, especially with regard to duration of follow-up, attrition rate, and specific reporting of follow-up in a subset of patients with BE-LGD. Moreover, the included studies were not entirely representative of the general population and community practice, with most studies being performed in tertiary-care referral centers. When we limited analysis to 11 high-quality studies, the overall pooled IR of EAC was 0.67% per year, with only moderate heterogeneity.

Besides limitations of individual studies, there were limitations of the overall analysis. First, the analyses were done assuming that the incidence rate is constant over time, which may not be accurate. However, this estimate is still the best available estimate that may be used in counseling of patients of BE-LGD. Second, this review was limited only to studies published in full text after complete peer review and did not include meeting proceedings. We also excluded articles not written in English. Third, in this review, we were unable to identify a high-risk subset of patients with BE-LGD who were likely to progress to EAC. This has been inadequately assessed in the current literature. One high-quality study reported a numerically higher risk of EAC in long-segment BE and multifocal LGD as well as persistent LGD, and this definitely warrants closer evaluation in future studies.[48] Patient-related characteristics such as age, smoking, and central fat deposits also need to be accounted for in identifying this high-risk subset who may benefit from aggressive surveillance and endoscopic eradication therapy. Finally, although we performed a systematic assessment of cause-specific mortality in patients with BE-LGD, our analysis was limited by the small number of studies and limited number of events. Current literature is clearly limited in addressing this key question, and larger studies are warranted. A previous cost-effectiveness analysis suggested that initial radiofrequency ablation would be the most cost-effective strategy rather than waiting for progression to BE-HGD, by using an annual progression rate of 0.5%.[70] However, that analysis did not adequately account for mortality from causes other than esophageal disease and was applicable only to patients with persistent BE-LGD that had been confirmed by expert pathologists. Better estimation of EAC-related mortality and mortality from conditions not related to esophageal disease in patients with BE-LGD would help determine the cost-effectiveness of endoscopic surveillance and endoscopic eradication therapy in these patients. A recent community-based, case-control study failed to identify a significant mortality benefit of endoscopic surveillance in patients with BE.[71]

In conclusion, we estimate that the annual rate of progression to EAC in patients with BE-LGD is 0.54%, albeit with wide variability across studies, with higher rates observed for studies in which the diagnostic prevalence of LGD is low (<15%). We observed a higher incidence of progression to EAC in studies when expert GI pathologists made the diagnosis of BE-LGD. The American Gastroenterological Association also acknowledges wide variability in the reported rate of progression to EAC in patients with BE-LGD. Ideally, all cases of BE-LGD require confirmation by an expert GI pathologist after resolution of esophageal inflammation.[1] Causes other than esophageal

disease appear to account for considerable mortality in these patients and should be carefully weighed when assessing cost-effectiveness of surveillance and eradication strategies. Future studies should focus on identifying a subset of patients with BE-LGD at high risk of progression to EAC as well as high risk of mortality from causes other than esophageal disease, with regard to patient-specific and BE-specific characteristics, to be able to target endoscopic and pharmacologic interventions.

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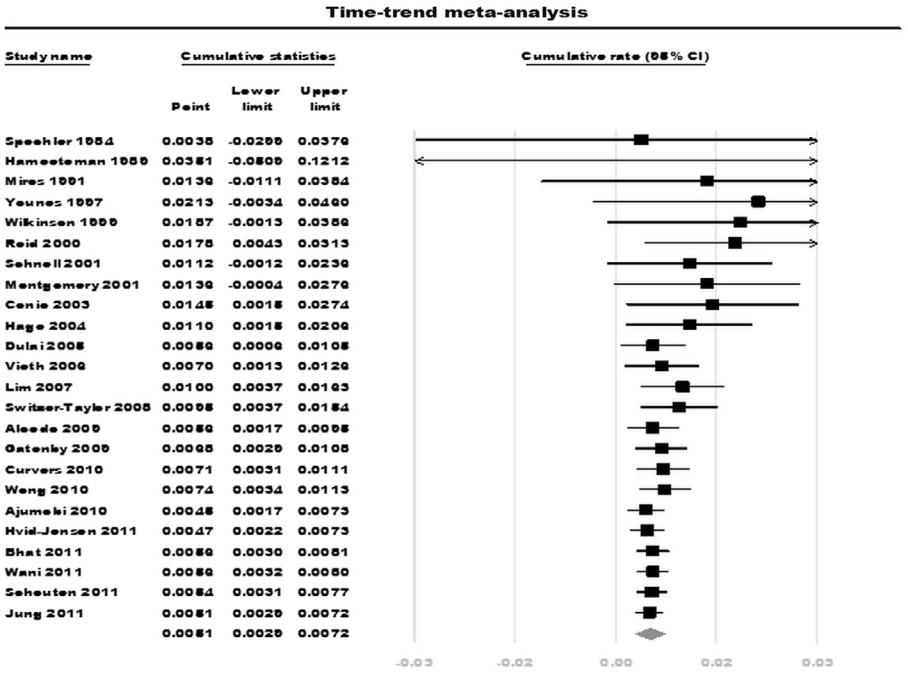
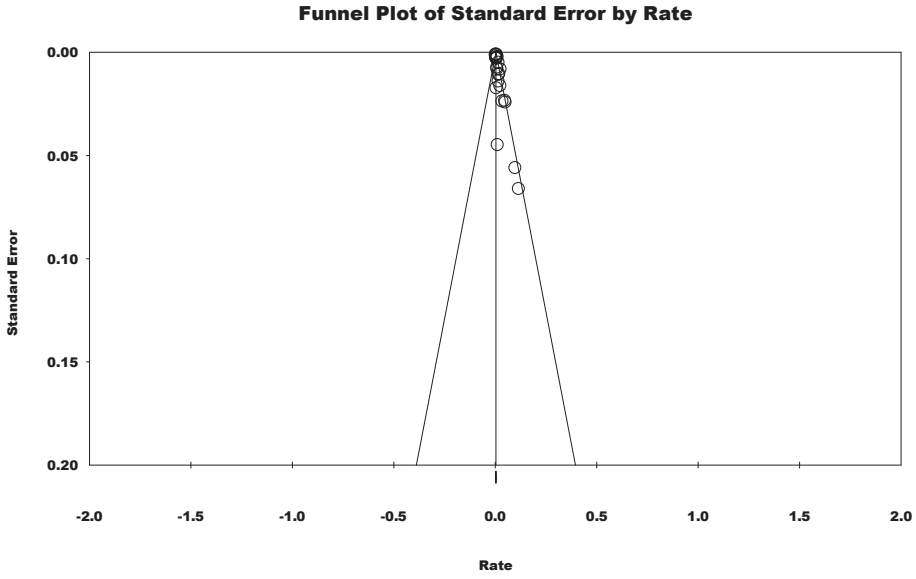
APPENDIX

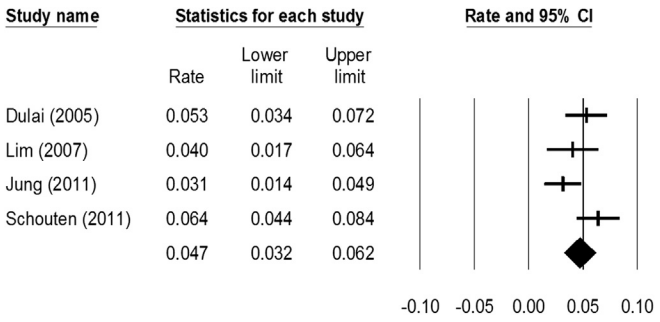
Data on the following were abstracted from individual studies: (a) study characteristics: primary author, time period of study/year of publication, country of the population studied; (b) BE specific characteristics: total number patients with BE, proportion with LGD, duration of follow-up (mean or median, total person-years of follow-up of patients with BE-LGD preferably, and if unavailable, then for the entire BE cohort) as well as attrition rate, number of patients with incident and/or prevalent LGD; whether diagnosis of LGD was made by single pathologist (expert or community) or by a consensus of pathologists; length of BE-LGD segment, unifocal or multifocal LGD and one-time or persistent LGD, where reported; and (c) outcome characteristics: number of patients with BE-LGD who developed EAC and who died of non-esophageal causes.



Supplementary Figure 1. Time-dependent cumulative meta-analysis of the incidence rate of progression to EAC in patients with Barrett's esophagus with low-grade dysplasia (starting with the earliest published study on the top, and with consecutive addition of studies by year of publication).



Supplementary Figure 2. Funnel plot assessing publication bias in primary analysis.



Supplementary Figure 3. Annual incidence of non-esophageal mortality in patients with Barrett's esophagus with low-grade dysplasia.