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CLINICAL/NARRATIVE REVIEW

Surveillance in Patients With Barrett's Esophagus for Early Detection of Esophageal Adenocarcinoma: A Systematic Review and Meta-Analysis

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OBJECTIVES: Although endoscopic surveillance of patients with Barrett's esophagus (BE) has been widely implemented for early detection of esophageal adenocarcinoma (EAC), its justification has been debated. This systematic review aimed to evaluate benefits, safety, and cost effectiveness of surveillance for patients with BE.

METHODS: MEDLINE, EMBASE, EconLit, Scopus, Cochrane, and CINAHL were searched for published human studies that examined screening practices, benefits, safety, and cost effectiveness of surveillance among patients with BE. Reviewers independently reviewed eligible full-text study articles and conducted data extraction and quality assessment, with disagreements resolved by consensus. Random effects meta-analyses were performed to assess the incidence of EAC, EAC/high-grade dysplasia (HGD), and annual stage-specific transition probabilities detected among BE patients under surveillance, and relative risk of mortality among EAC patients detected during surveillance compared with those not under surveillance.

RESULTS: A total of 51 studies with 11,028 subjects were eligible; the majority were of high quality based on the Newcastle–Ottawa quality scale. Among BE patients undergoing endoscopic surveillance, pooled EAC incidence per 1,000 person-years of surveillance follow-up was 5.5 (95% confidence interval (CI): 4.2–6.8) and pooled EAC/HGD incidence was 7.7 (95% CI: 5.7–9.7). Pooled relative mortality risk among surveillance-detected EAC patients compared with nonsurveillance-detected EAC patients was 0.386 (95% CI: 0.242–0.617). Pooled annual stage-specific transition probabilities from nondysplastic BE to low-grade dysplasia, high-grade dysplasia, and EAC were 0.019, 0.003, and 0.004, respectively. There was, however, insufficient scientific evidence on safety and cost effectiveness of surveillance for BE patients.

CONCLUSIONS: Our findings confirmed a low incidence rate of EAC among BE patients undergoing surveillance and a reduction in mortality by 61% among those who received regular surveillance and developed EAC. Because of knowledge gaps, it is important to assess safety of surveillance and health-care resource use and costs to supplement existing evidence and inform a future policy decision for surveillance programs.

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INTRODUCTION

Barrett's esophagus (BE) is defined as a change in the distal esophageal epithelium of any length that can be recognized as columnar-type mucosa at endoscopy and is confirmed to have intestinal metaplasia by biopsy of the tubular esophagus.[1] BE is the only known precursor to esophageal adenocarcinoma (EAC) via intermediate stages starting from nondysplastic BE (NDBE), followed by low-grade dysplasia (LGD) and high-grade dysplasia (HGD).[2,3] EAC has a poor prognosis as the majority of patients are diagnosed at the time of late-stage clinical presentation when curative treatments are less likely.[4] Therefore, patients diagnosed with BE are recommended to undergo endoscopic surveillance to monitor for potential disease progression. It has been shown that surveillance of BE patients identifies malignant progression at an earlier and less advanced stage, providing opportunities for curative interventions.[5–8] Previous population-based retrospective cohort studies demonstrated improved survival among surveillance-detected EAC patients compared with EAC patients not under surveillance who underwent diagnostic examination because of onset of symptoms.[5,8] A recent population-based retrospective cohort study also reported increased survival among patients with EAC who had a prior diagnosis of BE, even after correction for lead and length time bias.[9] In contrast, a recent case–control study in a community-based setting showed that current endoscopic surveillance practices for BE was not associated with the risk of EAC mortality.[10]

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Despite the reported benefits of surveillance for BE patients, justification for the surveillance is debatable. As surveillance endoscopy is expensive,[11] cost effectiveness of the surveillance has been questioned because of the low incidence rate of surveillance-detected EAC among BE patients.[12] In other words, patients who eventually ended up benefitting from the surveillance only accounted for a small proportion of BE patients undergoing surveillance.[12] In addition, risks associated with routine surveillance procedures, such as perforation, infection, and bleeding,[13] need to be taken into account. Furthermore, as BE patients undergoing surveillance are followed up for disease progression or regression, estimation of stage-specific transition probabilities between various stages of BE is an important aspect to consider in evaluating the effect of surveillance.

The aim of this study was to conduct a comprehensive search of existing literature and assemble in a systematic review up-to-date information regarding screening practice, benefits, safety, and cost effectiveness of surveillance for patients with BE.

METHODS

Search strategy and selection criteria. We conducted a systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[14] We searched electronic databases including MEDLINE, EMBASE, EconLit, Scopus, Cochrane, and CINAHL for human studies published before February 2015 that examined screening practices, benefits, safety, and costs of surveillance for patients diagnosed with BE. Detailed search strategy is shown in the Appendix and Table A1. The search was conducted by experienced research investigators. References of included studies were scanned for additional relevant studies. Inclusion criteria were: (i) peer-reviewed study with full-text available; (ii) BE patients who were verified to undergo subsequent surveillance; and (iii) reported disease progression/regression detected during surveillance, mortality risk among surveillance-detected EAC patients compared with EAC patients who have not undergone surveillance (i.e., nonsurveillance-detected EAC patients), safety, or cost effectiveness of surveillance based on person-level data. The definition of BE has evolved over time; the traditional definition required a segment of columnar epithelium to be at least 3 cm, whereas the current definition does not have restrictions regarding segment length. Studies based on both definitions were included. We excluded non-English studies, review studies, and case reports with <20 patients. Modeling studies (e.g., decision-analytic model) using hypothetical cohorts to assess cost effectiveness were excluded as our primary interest related to cost effectiveness was the evaluation based on person-level data. Finally, we checked for studies using the same set of patients and, if identified, only the study with more relevant information reported was included.

Study selection, data extraction, and quality assessment. Two reviewers (S.J.B. and W.Z.) screened each study independently by title and abstract based on the predefined eligibility criteria. Full texts of eligible studies were reviewed independently by two reviewers (Y.Q. and A.H.) for data extraction. Extracted information included author, year of publication, study location, study design, study population, number of patients undergoing surveillance included in final analyses, demographic characteristics (i.e., age, sex, and ethnicity), risk factors for BE (i.e., body mass index, smoking, alcohol consumption, long vs. short segment BE), and surveillance characteristics including method of surveillance, average time interval between endoscopies, number of endoscopic examinations received per patient, surveillance duration, and total person-years of surveillance follow-up. We also extracted data on disease progression/regression, safety assessment, and cost-effectiveness measures of surveillance, as well as number of deaths among surveillance-detected EAC patients and that among nonsurveillance-detected EAC patients, if available. Study quality was assessed by three reviewers (Y.Q., A.H., and H.-H.T.) independently. Cohort and case–control studies were assessed using the Newcastle–Ottawa scale,[15] and randomized controlled trials were evaluated based on Cochrane's risk of bias assessment tool.[16] See Appendix for details. Disagreements in study eligibility, data extraction, and quality assessment were resolved by consensus between the reviewers. Finally, two team members (Y.Q. and H.-H.T.) reviewed all data to ensure accuracy before analysis.

Meta-analysis and meta-regression. To estimate pooled incidence rate of EAC and/or EAC/HGD detected during surveillance, included studies had to meet the following criteria: (i) reported the number of incident EAC and/or EAC/HGD cases among a group of BE patients undergoing

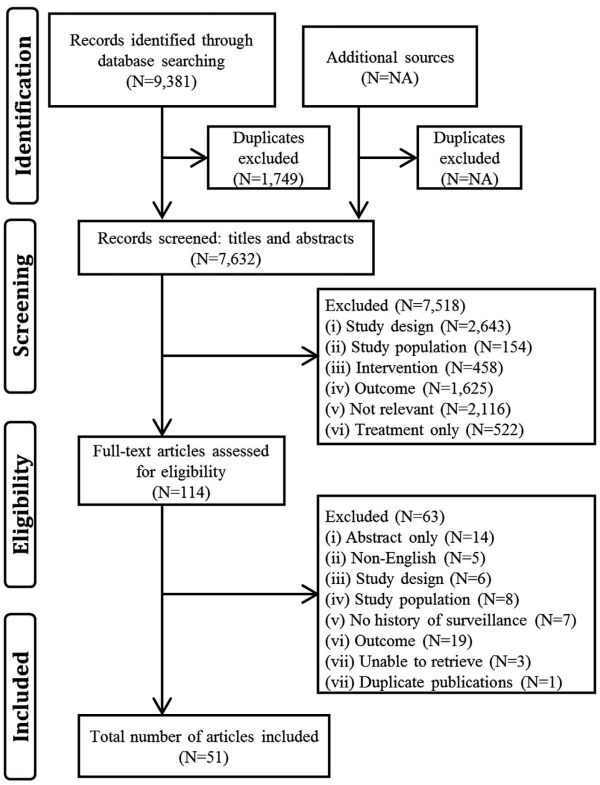

Figure 1 Identification of relevant literature. NA, not available.

Table 1 Study characteristics and baseline characteristics of patients under surveillance

First author, year	Setting	Study design	*N*	Age at BE diagnosis, years	Men, *N* (%)	LSBE, %	SSBE, %	Mean surveillance interval, months	Duration of surveillance, months	Number of endoscopies per patient	Person-years of surveillance
Robertson,[58]	United Kingdom	PCS	56	Mean, 62; range, 23–84	31 (55.4)	—	—	—	Mean, 35; range, 6–108	—	—
Ovaska,[31]	Finland	PCS	22	Mean, 59.2	—	100.0	0.0	—	Mean, 80.4; range, 36–144	—	166
Hameeteman,[32]	The Netherlands	PCS	50	Mean, 59.3; range, 28–78	30 (60.0)	100.0	0.0	—	Mean, 62.4; range, 18–168	—	260
Miros,[33]	Australia	PCS	81	Mean, 63.3	—	100.0	0.0	—	Mean (s.d.), 43.2 (20.4); range, 6–96	—	289
Williamson,[34]	United States	RCS	176	Mean, 56.0; range, 19–85	—	100.0	0.0	—	Median, 36	—	497
Iftikhar,[35]	United Kingdom	PCS	102	Mean (s.d.), 63 (13.5); range, 18–84	62 (60.8)	100.0	0.0	—	Mean (s.d.), 54 (12.5); range, 36–180	Mean, 3.7	462
Peters,[44]	United States	RCS	17	Median, 67; range, 42–80	16 (94.1)	82.4	17.6	6	Mean, 35.3; median, 36; range, 6–72	Mean, 5.5; median, 5; range, 2–15	50
Wright,[51]	United Kingdom	PCS	166	—	108 (65.1)	—	—	—	Male: mean, 32.4; female: mean, 34.8	Mean, 3.9	461
Ortiz,[36]	Spain	RCT	27	Median, 40; range, 12–78	20 (74.1)	100.0	0.0	—	Median, 48; range, 12–132	—	127
Ferraris,[37]	Italy	PCS	187	Range, 14–75	136 (72.7)	100.0	0.0	—	Mean, 36; range, 12–90	—	562
Sharma,[42]	United States	PCS	32	—	—	0.0	100.0	—	Mean (s.d.), 36.9 (5.4)	Mean, 3.25	98
Katz,[38]	United States	RCS	102	Median, 63; IQR, 35–78	85 (83.0)	100.0	0.0	—	Median, 57.6	—	563
van Sandick,[63]	The Netherlands	RCS	16	Mean, 64; range, 50–75	12 (75.0)	93.8	0.0	10	Mean, 48; median, 35.5; range, 10.2–55.6	—	64
Streitz,[50]	United States	RCS	136	—	—	—	—	17	—	Mean, 2.6	510
Teodori,[64]	Italy	PCS	30	Mean, 53; range, 32–69	18 (60.0)	—	—	—	Mean, 140.4; median, 156; range, 36–156	—	350
Schoenfeld,[65]	United States	PCS	123	Mean, 55	97 (78.9)	54.5	45.5	—	Mean, 48; range, 6–180	Mean, 2.2	495
Bani-Hani,[29]	United Kingdom	RCS	357	Male: mean, 58; range, 15–79. female: mean, 65; range, 28–79	207 (58.0)	95.5	4.5	—	Mean, 72; range, 24–187	—	1,293
Macdonald,[39]	United Kingdom	PCS	143	Mean, 57; range, 17–69	86 (60.1)	100.0	0.0	—	Mean, 52.8; range, 12–132	—	629
Nilsson,[30]	Sweden	RCS	199	Mean (s.d.), 58.7 (12.9); range, 20–88	139 (69.9)	67.3	15.6	13.2	Mean, 48; range, 6–166.8	Mean, 5.4; median, 4; range, 2–68	797
Rudolph,[66]	United States	PCS	235	—	—	70.6	29.4	—	Mean, 53.4	—	1,045
Reid,[67]	United States	PCS	327	Median, 62; range, 22–83	265 (81.0)	—	—	—	Median, 28.8; mean, 46.8; range, 0.6–156	Mean, 3.7	1,200
Fitzgerald,[49]	United Kingdom	RCS	96	Mean, 62; range, 28–89	71 (73.7)	—	—	—	Mean, 46.9	—	375
Corley,[8]	United States	RCS	15	Mean (95% CI), 61.4 (55.4–67.3)	14 (93.3)	—	—	9	Mean, 61.2	Median, 8; range, 1–17	—
Conio,[68]	Italy	PCS	166	Median, 59.9; range, 20–88	135 (81.3)	64.5	35.5	—	Mean, 66; range, 6–159.6	—	918
Hillman,[69]	Australia	PCS	353	Mean, 59.2; range, 18–89	249 (70.5)	—	—	—	Mean, 54.0; median 42; range 1–245	Mean, 4.2; median, 3; range, 1–40	1,588
Parrilla,[79]	Spain	RCT	43	Mean, 50; range, 12–78	33 (76.7)	—	—	—	Mean, 72; median 60; range, 12–216	—	258
Basu,[70]	United Kingdom	RCS	138	Mean (s.d.), 62.1 (10); range, 28–89	102 (73.9)	87.7	12.3	—	Mean, 34.8; range, 12–120	—	405
Fountoulakis,[5]	United Kingdom	RCS	17	Median, 70	11 (64.7)	—	—	—	Median, 72; range, 6–123	Median, 4; range, 2–11	—
Hage,[40]	The Netherlands	PCS	105	Mean, 63.4; range, 16–96	58 (55.2)	100.0	0.0	—	Mean, 152.4; range, 3.6–306	—	1,329
Meining,[71]	Germany	PCS	148	Mean (s.d.), 55.8 (10.6)	78 (52.7)	—	—	—	Mean, 30.5	—	376
Aldulaimi,[53]	United Kingdom	PCS	126	Median, 63 range, 22–87	96 (76.2)	—	—	—	Median, 24	Mean, 2.0	338
Murphy,[72]	United Kingdom	RCS	178	Mean, 57; range, 12–88	127 (71.4)	81.5	18.5	—	Mean, 40.8; range, 6–146.4	—	613
Dulai,[73]	United States	RCS	575	Mean (s.d.), 60.0 (12)	569 (99)	—	—	—	Mean, 57.9	Mean, 3.4	2,775
Oberg,[74]	Sweden	PCS	140	Median, 57.3; IQR, 47.6–67.5	104 (74.3)	—	—	16.8	Median, 69.6; IQR, 46.8–104.4	Mean, 5.5; median, 5; IQR, 4–6	946
Chang,[7]	United States	RCS	34	Median, 61; range, 35–80	28 (84.0)	91.2	8.8	—	Median, 36; range, 4–132	Mean, 10; range, 3–30	—
Gladman,[75]	United Kingdom	PCS	195	Male: mean (s.d.), 58.4 (12.9); range, 31–82. female: mean (s.d.), 66.8 (13.5); range, 37–96	108 (55.4)	89.7	10.3	—	Mean, 66	Mean, 2.9	1,068
Sharma,[43]	United States	PCS	618	Mean, 59	—	—	—	—	Mean, 49.44; range, 12–270	—	2,546
Vieth,[48]	Germany	RCS	748	Mean (s.d.), 60.9 (14.2); range, 15–94	507 (67.8)	42.1	32.9	—	Mean (s.d.), 78.2 (35.6)	Mean (s.d.), 2.6 (1.9); range, 1–14	4,874

Table 1 *(Continued)*

First author, year	Setting	Study design	*N*	Age at BE diagnosis, years	Men, *N* (%)	LSBE, %	SSBE, %	Mean surveillance interval, months	Duration of surveillance, months	Number of endoscopies per patient	Person-years of surveillance
Olithselvan,[46]	United Kingdom	RCS	121	Mean, 60.2	84 (69.5)	—	—	—	Mean, 42	Mean, 1.7	424
Switzer-Taylor,[41]	New Zealand	RCS	212	Mean (s.d.), 56.8 (11.9)	146 (68.9)	100.0	0.0	—	Mean (s.d.), 47.4 (36.12)	Mean, 3.5; range, 1–14	895
von Rahden,[47]	Germany	RCS	1,438	Mean (s.d.), 59.4 (12.7)	1028 (71.5)	—	—	—	Median, 24; range, 1–225	Median, 2; range, 2–15	—
Musana,[76]	United States	RCS	216	Mean (s.d.), 62.0 (15.3); median, 65.5; range, 17–94	165 (76.4)	51.9	24.5	—	Median, 38.4; range, 2–238.8	Mean, 3.3; range, 1–17	—
Martinek,[77]	Czech Republic	PCS	135	Mean (s.d.), 59.4 (15.2); range, 21–94	102 (75.6)	36.3	63.7	—	Mean (s.d.), 62.4 (27.6) range, 24–156	Mean (s.d.), 4.5 (3)	700
Alcedo,[12]	Spain	RCS	340	Mean (s.d.), 56.34 (17.19); median, 58; range, 17–88	269 (79.0)	56.5	43.5	—	Mean, 51; range, 0.2–317.2	—	1,323
Bright,[6]	Australia	RCS	405	Median, 66; range, 20–94	276 (68.2)	—	—	15	Median, 23; range, 1–40	—	776
Ramus,[78]	United Kingdom	RCS	817	Mean, 61.2	525 (64.3)	40.6	17.6	—	—	Mean, 5.9; range, 3–8	3,953
Ajumobi,[28]	United States	RCS	165	Mean (s.d.), 65.41 (11.41)	160 (97.0)	—	—	—	Median, 50; range: 3–204	—	—
Roberts,[52]	United Kingdom	RCS	302	—	—	100.0	0.0	14.6	Mean, 25.9; range, 9–63	Mean, 3.1; median, 3; range, 2–13	654
Abdalla,[45]	United States	RCS	146	Mean, 63.7	79 (54.1)	25.3	71.9	18.4	—	—	—
Corley,[10]	United States	CC	—	—	—	—	—	—	—	—	—
Verbeek,[59]	The Netherlands	RCS	452	Category, %, <60: 26; 60–80: 61; >80: 13	—	—	—	—	—	Median, 5; IQR, 3–7	—

BE, Barrett's esophagus; CC, case–control study; LSBE, long segment BE; IQR, interquartile range; NDBE, nondysplastic Barrett's esophagus; PCS, prospective cohort study; RCS, retrospective cohort study; RCT, randomized controlled trial; s.d., standard deviation; SSBE, short segment BE.

surveillance, and (ii) reported total person-years of surveillance follow-up or average surveillance duration, based on which total person-years of surveillance can be calculated. To test the hypothesis that surveillance is associated with a decreased risk of mortality among patients who ended up progressing to EAC, we calculated pooled relative risk of mortality based on studies that reported the number of deaths in both groups: (i) surveillance-detected EAC patients and (ii) nonsurveillance-detected EAC patients. Finally, we estimated pooled proportion and annual stage-specific transition probabilities of disease progression or regression by dividing the number of patients who progressed (e.g., NDBE → LGD, NDBE → HGD, or NDBE → EAC) or regressed to another stage (e.g., LGD → NDBE) observed at the end of surveillance follow-up by the total number of patients who were initially at a certain stage (e.g., NDBE) or by the total person-years of follow-up, respectively. We used random effects models to account for heterogeneity across studies.[17,18] For each model, we evaluated heterogeneity based on Cochran's Q statistics and I^2 statistics.[19–21] Publication bias was assessed using the Begg funnel plot and significance was tested based on Egger's test for funnel plot asymmetry.[22] The rate of type 1 error was set at $\alpha = 0.05$. For each meta-analysis, only studies that would contribute at least 20 patients to the analysis were included. We performed sensitivity analyses to assess robustness of the meta-analysis results. See Appendix for details. All meta-analyses were conducted using Comprehensive Meta-Analysis version 2.[23]

To explore source of heterogeneity both within and between studies included in meta-analyses for incidence rate of EAC and EAC/HGD, we conducted random effects meta-regression using a linear mixed model based on maximum likelihood method.[24,25] The meta-regression model included the natural log of incidence rate as the dependent variable and an explanatory variable, which had potential impact on the observed incidence rate, such as study design, time of publication (before 2000, 2000 and after), study location (United States, United Kingdom, other countries in Europe, Oceanian countries), average age, male percentage, and average surveillance duration. If the mean age or the mean surveillance duration of a study sample was not reported, it was approximated by the median, if available. Missing data were extrapolated by using the mean value of all the studies with reported data. Risk factors for progression to dysplasia and EAC, including ethnicity, smoking, and alcohol consumption, were not included in meta-regression because of limited number of studies with reported data. Statistical analysis of meta-regression was performed using SAS version 9.4 (Cary, NC).

Evidence synthesis on cost effectiveness and safety. We retrieved information on endoscopy-related adverse events such as perforation, infection, reaction to sedation, and bleeding. To enable meaningful comparison of cost-related findings across studies, we converted reported costs to US currency using Purchasing Power Parity[26] if required, and inflated costs to 2014 US dollars using the Consumer Price Index (Medical Care Services).[27]

RESULTS

Study characteristics. The search strategy yielded 9,381 studies, of which we identified 51 (0.5%) published studies involving 11,028 patients between 1988 and 2014 as eligible for evidence synthesis (Figure 1). A summary of the eligible studies is presented in Table 1. The majority ($n=44$, 86.2%) of the included cohort or case–control studies were assessed to be of high quality based on the Newcastle–Ottawa scale (Table A2).

The baseline study population in all studies consisted of patients with a previous diagnosis of BE. Apart from this, some studies had more specific inclusion criteria. For example, whereas most studies only excluded patients with neoplastic findings at the initial diagnosis, four studies further excluded patients who developed EAC/HGD within 6 months following their BE diagnosis as they were likely to have been carrying cancer at the time of the initial examination.[5,28–30] As the earlier definition of BE required segment length to be at least 3 cm, most studies published before or in 1998 reported only long segment BE patients.[31–38] Three studies published after 1998 enrolled only long segment BE patients.[39–41] In contrast, one study included only short segment BE patients in the analysis.[42] The criteria for considering a patient as having undergone surveillance differed across studies. Most studies required at least one subsequent surveillance endoscopy after the initial diagnosis, whereas three studies respectively required at least three surveillance endoscopies,[7] 0.5 years of surveillance follow-up,[30] and 1 year of surveillance follow-up.[43] Reported surveillance duration (mean or median) ranged from 23 to 152 months.[4,33] Reported average surveillance interval ranged from 6 to 18 months.[44,45] The mean number of endoscopic examinations received per patient ranged from 2 to 10,[7,46] and the median varied from 2 to 8.[8,47] Total person-years of surveillance follow-up reported in each included study ranged from 50 to 4,874.[44,48]

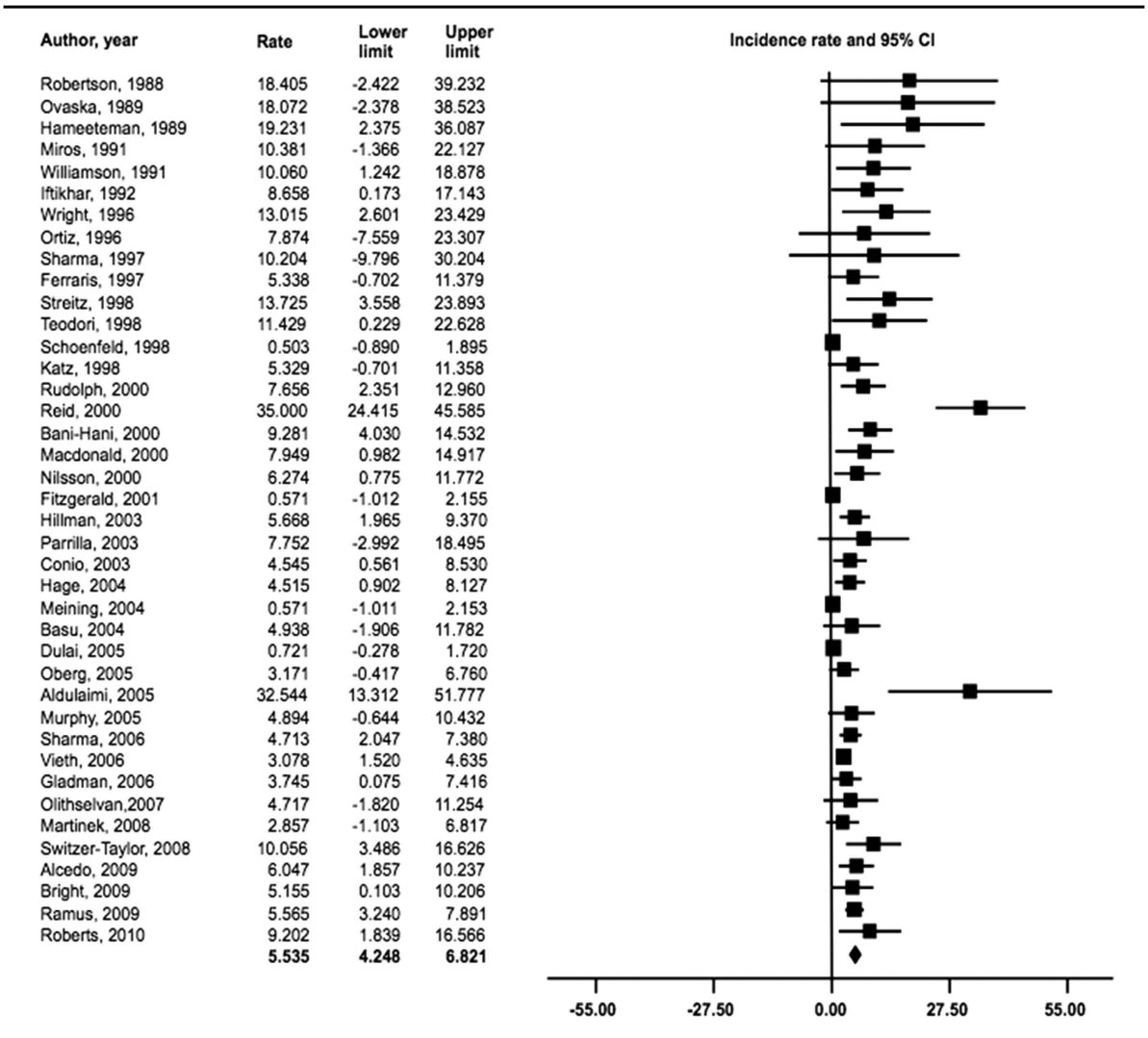

Figure 2 Incidence of esophageal adenocarcinoma (EAC) detected among Barrett's esophagus (BE) patients undergoing surveillance. Assessment of heterogeneity: $I^2=74.0\%$, $P<0.001$. CI, confidence interval.

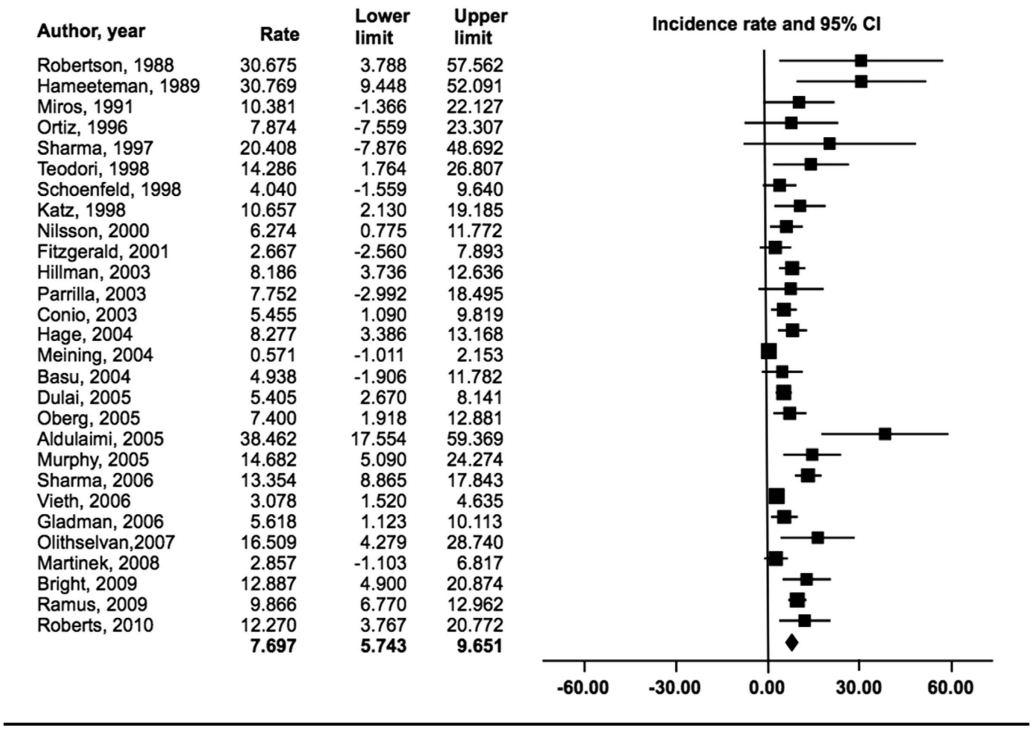

Figure 3 Incidence of esophageal adenocarcinoma/high-grade dysplasia (EAC/HGD) detected among Barrett's esophagus (BE) patients undergoing surveillance. Assessment of heterogeneity: $I^2 = 74.0\%$, $P < 0.001$. CI, confidence interval.

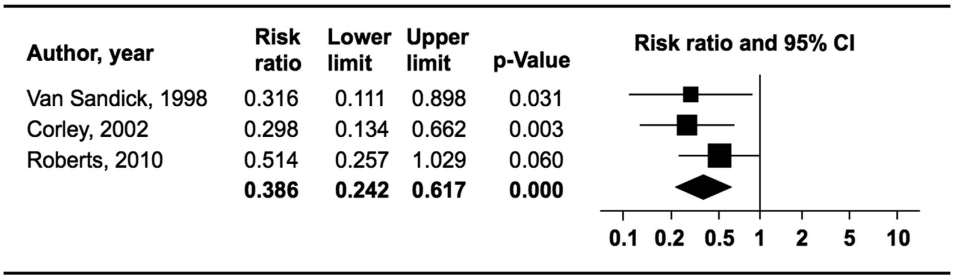

Figure 4 Relative risk of mortality associated with previous surveillance status among cancer patients. Assessment of heterogeneity: $I^2 = 0\%$, $P = 0.550$. CI, confidence interval.

The method of surveillance was endoscopy followed by biopsy in most included studies except for the surveillance program in one study that did not have mandatory biopsy protocol.[29]

Meta-analyses. Of the included studies, 40 studies, including 8,512 BE patients undergoing surveillance, met the inclusion criteria for meta-analysis of incidence rate of EAC (Figure 2). The estimated pooled incidence rate was 5.5 (95% confidence interval (CI): 4.2–6.8) EAC cases per 1,000 person-years of surveillance follow-up that was equivalent to an annual risk of 0.55%. Heterogeneity across these studies was identified ($I^2 = 74.0\%$, $P < 0.001$) and publication bias was detected by the funnel plot and Egger's test ($P < 0.001$; Figure A1).

Furthermore, 28 studies, including 6,109 BE patients, met the inclusion criteria for meta-analysis of incidence rate of EAC/HGD (Figure 3). The estimated pooled incidence rate was 7.7 (95% CI: 5.7–9.7) EAC/HGD cases per 1,000 person-years of surveillance follow-up. Heterogeneity was identified across these studies ($I^2 = 74.0\%$, $P < 0.001$). The funnel plot and Egger's test suggested presence of publication bias ($P < 0.001$; Figure A2).

Moreover, three studies were included in the meta-analysis of relative risk of mortality associated with previous surveillance among EAC patients (Figure 4), yielding a pooled relative mortality risk of 0.386 (95% CI: 0.242–0.617). No evidence of heterogeneity across studies ($I^2 = 0\%$, $P = 0.550$) or publication bias ($P = 0.517$; Figure A3) was identified. The observed I^2 value of 0% is likely because of the small number of included studies.

Table 2 summarizes pooled proportions and annual transition probabilities of patients (NDBE and LGD) who progressed

Table 2 Stage-specific transition probabilities

Progression/ regression	Proportion[a]			Annual transition probability[b]		
	Pooled estimate (95% CI)	Assessment of heterogeneity	No. of included studies (reference numbers)	Pooled estimate (95% CI)	Assessment of heterogeneity	No. of included studies (reference numbers)
NDBE → LGD	0.096 (0.044–0.195)	$I^2 = 93\%$; $P < 0.001$	7 (8, 30, 34, 37,42, 44, 70)	0.019 (0.004–0.035)	$I^2 = 92\%$; $P < 0.001$	4 (8, 30, 44, 70)
NDBE → HGD	0.016 (0.009–0.028)	$I^2 = 0\%$; $P = 0.614$	5 (8, 34, 42, 44, 70)	0.003 (0.001–0.005)	$I^2 = 0\%$; $P = 0.540$	3 (8, 44, 70)
NDBE → EAC	0.027 (0.016–0.045)	$I^2 = 27\%$; $P = 0.243$	5 (8, 30, 34, 44, 70)	0.004 (0.001–0.008)	$I^2 = 41\%$; $P = 0.166$	4 (8, 30, 44, 70)
LGD → HGD	0.042 (0.000–0.088)	$I^2 = 26\%$; $P = 0.259$	3 (8, 34, 70)	NA		
LGD → EAC	0.032 (0.001–0.063)	$I^2 = 0\%$; $P = 0.714$	4 (8, 26, 34, 70)			
LGD → NDBE	0.102 (0.005–0.200)	$I^2 = 86\%$; $P < 0.001$	4 (8, 26, 34, 70)			

CI, confidence interval; EAC, esophageal adenocarcinoma; HGD, high-degree dysplasia; LGD, low-degree dysplasia; NA, not applicable as total person-years of follow-up among LGD patients were not retrievable from individual studies; NDBE, nondysplastic Barrett's esophagus.
[a]Pooled proportion was estimated by dividing the number of patients who progressed (e.g., NDBE → LGD, NDBE → HGD, or NDBE → EAC) or regressed to another stage (e.g., LGD → NDBE) observed at the end of surveillance follow-up by the total number of patients who were initially at a certain stage (e.g., NDBE).
[b]Pooled annual stage-specific transition probability was estimated by dividing the number of patients who progressed (e.g., NDBE → LGD, NDBE → HGD, or NDBE → EAC) or regressed to another stage (e.g., LGD → NDBE) observed at the end of surveillance follow-up by the total person-years of follow-up who were initially at a certain stage (e.g., NDBE).

or regressed to another stage. These estimates were not obtained for HGD patients as we were not able to identify more than one study with over 20 HGD patients detected at the beginning of or any time during follow-up. We found higher proportion of LGD patients than NDBE patients who progressed to EAC (3.2% vs. 2.7%), or to HGD (4.2% vs. 1.6%). However, there were no significant differences in these proportions. The proportion of LGD patients who regressed to NDBE was 10.2%. Pooled annual transition probabilities to LGD, HGD, and EAC among NDBE patients were estimated to be 0.019, 0.003, and 0.004, respectively.

Meta-regression. In the meta-regression (Table 3), only year of publication was found to be associated with the incidence rate of EAC detected during surveillance, suggesting that studies published before 2000 demonstrated a higher rate of EAC than studies published in or after 2000 ($P = 0.049$). However, no factors were found to be associated with the incidence rate of EAC/HGD.

Reported costs and safety. Cost effectiveness of surveillance for BE patients was estimated from a limited number of studies based on various measures. Cost of surveillance for detecting one case of EAC was reported by 4 studies, with an estimate of $17,825,[49] $71,202,[30] $71,415,[50] and $57,927 for men and $163,863 for women.[51] Two studies reported costs of both detection and treatment per life year gained attributable to surveillance, with an estimate of $7,816 (ref. 50) and $6,654.[52] Two studies evaluated cost per cancer cured and yielded a cost of $16,374, which only considered endoscopic costs,[53] and $156,922, which considered both detection and treatment costs.[50] We found only one study that assessed complications of surveillance procedure that reported no endoscopic esophageal perforations during the surveillance examinations for 136 patients.[50]

DISCUSSION

In this systematic review and meta-analysis, we identified an incidence rate of 5.5 EAC cases and 7.7 EAC/HGD cases per 1,000 person-years of follow-up among BE patients under surveillance. In addition, our meta-analysis showed a reduction in mortality risk among EAC patients by 61% attributable to prior surveillance. We also identified annual stage-specific transition probabilities of 0.019, 0.003, and 0.004 among NDBE patients who progress to LGD, HGD, and EAC, respectively. Furthermore, we identified a knowledge gap regarding safety assessment of endoscopic procedures as well as insufficient scientific evidence for cost effectiveness of surveillance for BE patients.

Three previous systematic review studies assessed pooled incidence rate of EAC among BE patients and reported an incidence rate of 6.1, 6.3, and 7 per 1,000 person-years of follow-up, respectively,[54–56] and these were generally consistent with the estimate from our meta-analysis. However, none of these studies assessed stage-specific transition probabilities among BE patients. To our knowledge, this is the first review study to gain insights into stage-specific transition probabilities among BE patients under surveillance. Stage-specific transition probabilities are important outcomes

Table 3 Meta-regression results for the incidence rate of EAC and that of EAC/HGD

Variable	β	s.e.	*P*-value	RR (95% CI)
EAC				
Study design				
RCT	Reference	—	—	1
PCS	0.103	0.725	0.888	1.108 (0.255–4.810)
RCS	– 0.292	0.729	0.691	0.747 (0.170–3.271)
Year of publication				
2000–2014	Reference	—	—	1
1988–1999	0.526	0.259	0.049	1.692 (1.002–2.859)
Country of study				
United States	Reference	—	—	1
United Kingdom	0.028	0.324	0.931	1.028 (0.533–1.984)
Other countries in Europe	– 0.294	0.328	0.376	0.745 (0.383–1.449)
Oceanian countries	– 0.077	0.435	0.861	0.926 (0.383–2.238)
Average age	0.011	0.035	0.756	1.011 (0.942–1.085)
Male percentage	– 0.014	0.015	0.335	0.986 (0.956–1.016)
Average surveillance duration	– 0.004	0.005	0.346	0.996 (0.986–1.005)
EAC or HGD				
Study design				
RCT	Reference	—	—	1
PCS	0.351	0.714	0.627	1.420 (0.327–6.179)
RCS	0.067	0.718	0.927	1.069 (0.243–4.695)
Year of publication				
2000–2014	Reference	—	—	1
1988–2000	0.578	0.297	0.063	1.783 (0.968–3.285)
Country of study				
United States	Reference	—	—	1
United Kingdom	0.373	0.351	0.300	1.451 (0.703–2.997)
Other countries in Europe	– 0.240	0.350	0.500	0.787 (0.382–1.620)
Oceanian countries	0.108	0.450	0.813	1.114 (0.440–2.820)
Average age	0.022	0.034	0.524	1.022 (0.953–1.098)
Male percentage	– 0.015	0.013	0.258	0.985 (0.959–1.012)
Average surveillance duration	–0.005	0.004	0.226	0.995 (0.986–1.003)

CI, confidence interval; EAC, esophageal adenocarcinoma; HGD, high-degree dysplasia; PCS, prospective cohort study; RCS, retrospective cohort study; RCT, randomized controlled trial; RR, relative risk.

for BE surveillance programs as an essential benefit of surveillance is timely detection of disease progression to precancer stages, providing opportunities for applying appropriate interventions such as endoscopic mucosal resection and esophagectomy to prevent further malignant progression. Our estimate of annual progression from NDBE to EAC (0.004) shows minimal risk of disease progression similar to a recent prospective cohort study evaluating the performance of genetic biomarkers and clinical factors for disease progression in NDBE surveillance cohort (0.006).[57] In addition, we demonstrated the benefit of surveillance by showing a decreased risk of mortality among surveillance-detected EAC patients compared with those not under surveillance.

Furthermore, whereas previous review studies raised doubts over the cost effectiveness of the surveillance based on a low incidence rate of EAC among BE patients, this systematic review aimed to retrieve scientific evidence on cost-effectiveness evaluations. Although cost effectiveness is a focus of the controversy, we were only able to identify a limited number of studies that assessed cost effectiveness based on person-level data. Moreover, the cost-effectiveness measure reported varied from study to study, including cost per cancer detected, cost per cancer cured, and incremental cost per life-year gained attributable to the surveillance. As a result, there was insufficient evidence base to allow a meta-analysis to be performed. In addition, among those studies that evaluated cost per cancer detected, the reported cost varies considerably. This may be explained by differences in the incidence rate of cancer, average number of biopsies taken per endoscopy, and average intervals between surveillance endoscopies across study samples. Our findings highlight the need for additional studies to be conducted to evaluate the real-world cost effectiveness of surveillance for patients with BE to provide evidence of its true value in delivering expected outcomes.

The strength of our study is that we carried out a comprehensive systematic review of existing literature to capture the practice, benefit, cost effectiveness, and safety of the surveillance for BE patients. In addition, the robustness of the meta-analysis results was confirmed through sensitivity analyses. Furthermore, most included studies demonstrated similarity in major patient demographic characteristics such as white, male, and elderly, and therefore the study results are potentially generalizable to other populations with similar characteristics. Finally, the scientific evidence reviewed in this study will inform decision making in clinical practice and public health policies to reduce the burden of disease through effective interventions.

There are several limitations of our review study. First, the included studies were published across a wide time span, i.e., from 1988 (ref. 58) to 2014,[59] during which the definition of BE has evolved, and technological advances may

have improved the diagnostic capability of screening and the effectiveness of medication and treatment options available for BE patients. This point was further demonstrated by the meta-regression that indicated that year of publication constituted a source of heterogeneity for the incidence rate of EAC. Second, there were limited number of studies that met the inclusion criteria for the meta-analyses for the stage-specific transition probabilities and the relative risk of mortality among surveillance-detected EAC patients compared with EAC patients without having received surveillance. Third, pooled annual stage-specific transition probabilities for LGD and HGD patients were not calculated because of the lack of person-years of follow-up among these patients reported from individual studies. Finally, the existence of a number of guidelines for surveillance of BE patients[60–62] as well as the variation in the degree of clinician adherence to guidelines and patient compliance would lead to heterogeneity in surveillance practices that may limit the comparability across studies.

In conclusion, we identified a low incidence rate of EAC among BE patients undergoing surveillance. Although cost effectiveness is the focus of the debate, this important issue remains insufficiently reported and needs future comparative studies to provide further insights. In addition, we demonstrated that certain groups of BE patients do benefit from the surveillance as surveillance-detected EAC patients are at a lower risk of mortality. Although surveillance in BE patients has been a controversial issue, our findings provide scientific evidence of detection of precancerous LGD and HGD to support the practice of endoscopic surveillance recommended by multiple gastroenterology societies. We call for future studies to identify subgroups of BE patients who are at high risk of malignant progression and thus most likely to benefit from the surveillance. Therefore, more targeted surveillance programs yielding favorable cost effectiveness can be accordingly established.

CONFLICT OF INTEREST

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Surveillance of patients with Barrett's esophagus (BE) has been widely implemented to detect dysplasia and early esophageal adenocarcinoma (EAC).
- ✓ Benefits, safety, and cost effectiveness of current endoscopic surveillance strategies remain controversial.

WHAT IS NEW HERE

- ✓ The meta-analysis confirmed a low incidence rate of EAC among patients with BE under endoscopic surveillance.
- ✓ The meta-analysis demonstrated 61% reduced risk of mortality among surveillance-detected EAC patients compared with nonsurveillance-detected EAC patients.
- ✓ Annual mean stage-specific transition probability from nondysplastic BE to EAC shows minimal risk of disease progression.
- ✓ We identified insufficiency and discrepancies in the evidence of cost effectiveness of endoscopic surveillance of BE.

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APPENDIX: Surveillance in patients with barrett's esophagus for early detection of esophageal adenocarcinoma: a systematic review and meta-analysis

METHODS

Search strategy. We identified relevant studies using the following search strategy: (GERD/BE/EAC or synonyms) AND (screening/surveillance/diagnostic tests or synonyms) AND (safety/efficacy/cost or synonyms) AND (treatment outcomes/disease state or synonyms). See Table A1 for more detailed search strategies.

Sensitivity analysis. We performed sensitivity analyses to assess robustness of the meta-analysis results. First, as the included studies were conducted across a variety of medical settings from various countries and regions, there was inevitably variation in the method of surveillance adopted between studies. Most surveillance programs reported utilizing endoscopy followed with biopsies as the surveillance protocol; however, a few studies included no mandatory biopsy protocol in the surveillance practice. Considering the potential impact of different surveillance methods on the detection of disease progression, we repeated the meta-analysis by excluding studies that did not incorporate biopsy protocol. Second, the currently accepted definition of BE does not have a requirement regarding segment length (1) studies that were known to include only long segment BE (LSBE, segment length ≥ 3 cm) patients or only short segment BE (SSBE, segment length <3 cm) patients are thus not representative of the whole BE patient population. We therefore conducted sensitivity analysis excluding studies that were known to contain only LSBE patients or only SSBE patients. Third, to account for the potential impact of study quality on pooled estimates, we conducted sensitivity analyses excluding studies with Newcastle–Ottawa scale (NOS) quality scores lower than 6, 7, or 8, respectively. Finally, we repeated the meta-analysis removing one study at a time, and excluding the studies that were at the extremes in the forest plot.

RESULTS

Study characteristics. Among the 51 included published studies between 1988 and 2014, the majority were conducted in the United States ($n=16$) and United Kingdom ($n=14$), whereas others took place in the Netherlands ($n=4$), Italy ($n=3$), Spain ($n=3$), Australia ($n=3$), Germany ($n=3$), Sweden ($n=2$), and one study in each of the following: Finland, New Zealand, and Czech Republic. The majority of these studies were published between 2000 and 2014 ($n=35$). Most studies were cohort studies (26 retrospective cohort studies and 22 prospective cohort studies, $n=48$, 94.1%), whereas two studies were randomized controlled trials and only one study was a case–control study. The majority ($n=44$, 86.2%) of the included cohort or case–control studies were assessed to be high quality as they were awarded six or higher points (out of a maximum of nine points) based on the NOS quality score (Appendix Table A2). Assessment of risk of bias based on Cochrane's tool for the two randomized controlled trials is summarized in Appendix Table A3.

Among BE patients undergoing surveillance, the overall ($n=33$) mean age was 60 years (range: 50–65 years) (28,44), the median age reported by 12 studies ranged from 40 to 70 years (5,36), and the overall ($n=44$) male proportion was 71.7% (range: 52.7–99.0%) (45,46). Information on ethnicity, body mass index (BMI), smoking, and alcohol consumption was reported in a limited number of studies. Among eight studies (8,28,45–50), Caucasians were the vast majority of Barrett's esophagus (BE) patients enrolled in the surveillance program, with an overall proportion of 90.9% (range: 80.8–100%) (8,45,49,50). Three studies reported data on mean BMI ranging from 28 to 29 kg/m^2 (45,46,49) and two studies reported BMI categories (obesity proportion, range: 40.8–41.2%) (28,50). Percentages of smokers (former or active smokers) among BE patients undergoing surveillance were reported by nine studies (8,12,34,38,45,46,49-51), ranging from 30 to 93% (8,34). Current alcohol consumption among BE patients under surveillance was obtained from six studies (12,34,38,45,46,50), with the percentages of drinkers ranging from 24.4 to 81.3% (12,50).

Sensitivity analysis. Sensitivity analyses generally showed similar results as the initial estimates, demonstrating the robustness of the meta-analysis results. Regarding the method of surveillance, we found one study in which the surveillance endoscopies did not have mandatory biopsy protocols, whereas the surveillance practice in the remaining studies were based on endoscopies along with biopsies (22). A sensitivity analysis was conducted excluding this study from the meta-analysis that resulted in a similar pooled incidence rate of 5.4 (95% confidence interval (CI): 4.1–6.7) esophageal adenocarcinoma (EAC) cases detected per 1,000 person-years of surveillance follow-up, with significant heterogeneity ($I^2=73.5\%$, $P<0.001$). Sensitivity analyses excluding studies that were known to contain only LSBE patients or only SSBE patients from the meta-analyses led to a pooled incidence rate of 4.9 (95% CI: 3.5–6.3) EAC cases per 1,000 person-years based on 27 studies, with significant heterogeneity ($I^2=78.7\%$, $P<0.001$), and an incidence rate of 7.0 (95% CI: 4.9–9.1) EAC/HGD cases per 1,000 person-years based on 21 studies, with significant heterogeneity ($I^2=77.3\%$, $P<0.001$). Sensitivity analyses excluding studies with NOS quality scores lower than 6, 7, or 8, removing one study at a time, or excluding studies demonstrating extreme estimates on the forest plot did not lead to significantly different results from the original pooled estimates.

Table A1 Search strategy

BE	1	Barrett Esophagus/
	2	(barrett$ adj5 (oesophag$ or esophag$)).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
EAC	3	Esophageal Neoplasms/
	4	((esophag$ or oesophag$) adj5 adenocarcinoma).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
	5	exp Adenocarcinoma/
	6	exp Esophagus/
	7	5 and 6
	8	(column* adj3 (epithelium* or esophag* or oesophag*)).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
BE	9	((long adj segment) or LSBE or LSBO).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
	10	((short adj segment) or SSBE or SSBO).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
EAC	11	((interstitial or "low grade" or "high grade") and dysplasia).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
	12	((esophag* or oesophag*) adj5 (cancer* or neoplasm*)).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
BE	13	1 or 2 or 9 or 10
EAC	14	3 or 4 or 7 or 8 or 11 or 12
BE and EAC	15	13 and 14
Screening	16	mass screening.mp. or exp Mass Screening/
	17	surveill*.mp.
	18	exp Public Health Surveillance/ or exp Population Surveillance/
	19	endoscop*.mp.
	20	exp Endoscopy/ or exp Endoscopy, Gastrointestinal/ or exp Endoscopy, Digestive System/
	21	exp Image-Guided Biopsy/ or exp Biopsy/
	22	biops*.mp.
	23	exp Genetic Testing/
	24	(biomarker* or (bio* adj3 marker*)).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
	25	((antibody or cell or cancer or gene*) adj5 (test* or screen* or surveill*)).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
	26	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
Treatment	27	proton pump inhibitors/ or dexlansoprazole/ or esomeprazole/ or lansoprazole/ or omeprazole/ or rabeprazole/
	28	(proton pump inhibitor* or dexlansoprazole or esomeprazole or lansoprazole or omeprazole or rabeprazole).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
	29	pantoprazole.mp.
	30	"salvianolic acid A".mp.
	31	scopadulciol.mp.
	32	Timoprazole.mp. or exp 2-Pyridinylmethylsulfinylbenzimidazoles/
	33	xanthoangelol.mp.
	34	"endoscopic mucosal resection".mp.
	35	exp Photochemotherapy/
	36	photo*therapy.mp.
	37	cryotherapy.mp. or exp Cryotherapy/
	38	esophagectomy.mp. or exp Esophagectomy/
	39	((radiofrequency or endoscop*) adj3 ablation).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
	40	exp Fundoplication/ or "nissen fundoplication".mp.
	41	nsaid.mp. or exp Anti-Inflammatory Agents, Non-Steroidal/
	42	Histamine H2 Antagonists/
	43	Cimetidine.mp. or exp Cimetidine/
	44	Burimamide.mp. or exp Burimamide/
	45	famotidine.mp. or exp Famotidine/
	46	exp Metiamide/ or Metiamide.mp.
	47	Nizatidine.mp. or exp Nizatidine/
	48	Ranitidine.mp. or exp Ranitidine/
	49	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48
Economics	50	exp Economics, Pharmaceutical/ or exp Economics, Medical/ or exp Economics/ or exp Economics, Hospital/ or exp Economics, Dental/ or exp Economics, Nursing/
	51	cost*.mp. or exp "Costs and Cost Analysis"/ or exp Cost-Benefit Analysis/ or "Cost of Illness"/
	52	fees.mp. or exp "Fees and Charges"/
	53	(economic$ or pharmacoeconomic$ or price$ or pricing).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
	54	50 or 51 or 52 or 53
Epidemiology	55	incidence.mp. or exp Incidence/
	56	prevalence.mp. or exp Prevalence/
	57	exp Risk Factors/ or risk.mp. or exp Risk/
	58	epidemiol$.mp. or exp Epidemiology/
	59	55 or 56 or 57 or 58
Screening, Treatment, Economics, Epidemiology	60	26 or 49 or 54 or 59
(BE/EAC) AND (Screening, Treatment, Economics, Epidemiology)	61	15 and 60

BE, Barrett's esophagus; EAC, esophageal adenocarcinoma.

Table A2 Newcastle–Ottawa scale for study quality

Study	Selection				Comparability	Outcome/exposure			Total score
	1	2	3	4	1	1	2	3	
Robertson *et al.*[58]	★		★	★	★	★	★	★	7
Ovaska *et al.*[31]	★		★	★	★	★	★	★	7
Hameeteman *et al.*[32]	★		★	★	★★	★	★	★	8
Miros *et al.*[33]	★		★	★	★	★	★	★	7
Williamson *et al.*[34]	★	★	★	★	★★	★	★	★	9
Iftikhar *et al.*[35]	★		★	★	★	★	★	★	7
Peters *et al.*[44]		★	★	★	★★	★	★	★	8
Wright *et al.*[51]	★	★	★	★	★	★	★	★	8
Ferraris *et al.*[37]	★			★			★		3
Sharma *et al.*[42]	★		★		★★	★			5
Katz *et al.*[38]	★		★	★	★★	★	★	★	8
Van Sandick *et al.*[63]		★	★	★	★★	★		★	7
Streitz *et al.*[50]	★		★		★	★	★	★	6
Teodori *et al.*[64]	★		★	★	★	★	★	★	7
Schoenfeld *et al.*[65]			★	★	★★	★			5
Bani-Hani *et al.*[29]	★		★	★	★	★	★		6
Macdonald *et al.*[39]	★	★	★	★	★★	★	★	★	9
Nilsson *et al.*[30]	★		★	★	★★	★	★	★	8
Rudolph *et al.*[66]	★		★	★	★★	★	★		7
Reid *et al.*[67]	★		★	★	★	★	★		6
Fitzgerald *et al.*[49]	★	★	★	★	★★	★	★	★	9
Corley *et al.*[8]	★	★	★	★	★★	★	★	★	9
Conio *et al.*[68]	★		★	★	★	★	★	★	7
Hillman *et al.*[69]	★		★	★	★	★	★	★	7
Basu *et al.*[70]	★		★	★	★★	★	★	★	8
Fountoulakis *et al.*[5]	★	★	★	★	★★	★	★		8
Hage *et al.*[40]	★		★	★	★★	★	★	★	8
Meining *et al.*[71]	★		★	★	★★	★			6
Aldulaimi *et al.*[53]	★	★		★	★	★	★		6
Murphy *et al.*[72]	★		★	★	★★	★	★	★	8
Dulai *et al.*[73]	★		★	★	★★	★	★		7
Oberg *et al.*[74]	★		★	★	★★	★	★		7
Chang *et al.*[7]	★		★	★		★	★	★	6
Gladman *et al.*[75]	★		★	★	★	★	★	★	7
Sharma *et al.*[43]	★		★	★	★	★	★	★	7
Vieth *et al.*[48]	★		★	★	★★	★	★	★	8
Olithselvan *et al.*[46]	★		★	★	★	★	★	★	7
Switzer-Taylor *et al.*[41]		★	★	★	★	★	★	★	7
Von Rahden *et al.*[47]	★		★	★		★			4
Musana *et al.*[76]	★		★	★	★★	★	★		7
Martinek *et al.*[77]	★		★	★	★★	★	★	★	8
Alcedo *et al.*[12]	★		★	★	★★	★	★		7
Bright *et al.*[6]	★		★	★	★	★		★	6
Ramus *et al.*[78]	★	★	★	★	★★	★	★	★	9
Ajumobi *et al.*[28]	★	★	★	★	★	★	★		7
Roberts *et al.*[52]	★	★	★	★	★	★	★	★	8
Abdalla *et al.*[45]	★		★	★	★★	★	★		7
Corley *et al.*[10]	★	★	★	★	★	★	★	★	8
Verbeek *et al.*[59]		★	★	★	★	★			5

Table A3 Cochrane's tool for assessing risk of bias

Study	Sequence generation	Allocation concealment	Blinding of participants, personnel, and outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Ortiz *et al.*[36]	Low	Unclear	Unclear	High	Low	Low
Parrilla *et al.*[79]	Low	Low	Unclear	High	Low	Low

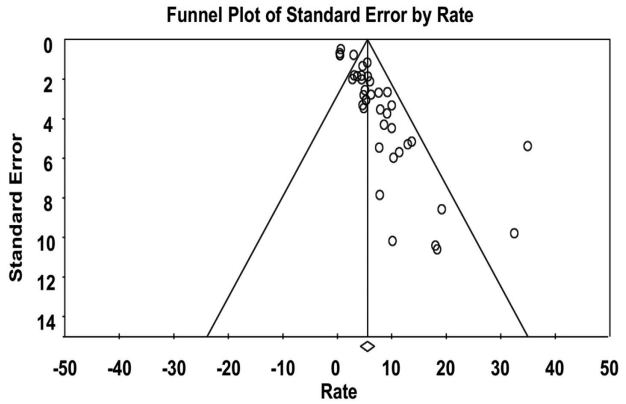

Figure A1 Funnel plot: meta-analysis for incidence of esophageal adenocarcinoma (EAC) among Barrett's esophagus (BE) patients undergoing surveillance. Egger's test for funnel plot asymmetry: $P < 0.001$.

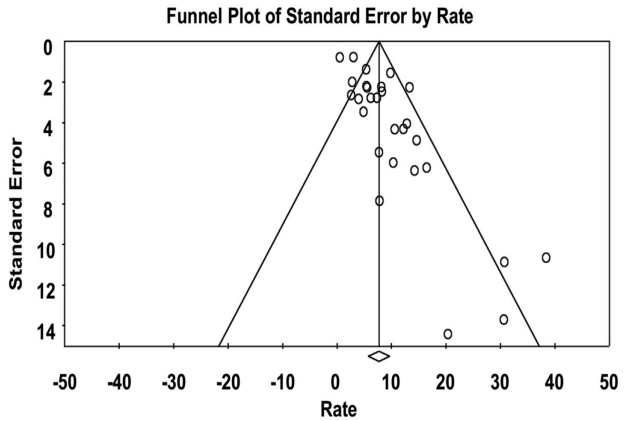

Figure A2 Funnel plot: meta-analysis for incidence of esophageal adenocarcinoma/high-grade dysplasia (EAC/HGD) among Barrett's esophagus (BE) patients undergoing surveillance. Egger's test for funnel plot asymmetry: $P < 0.001$.

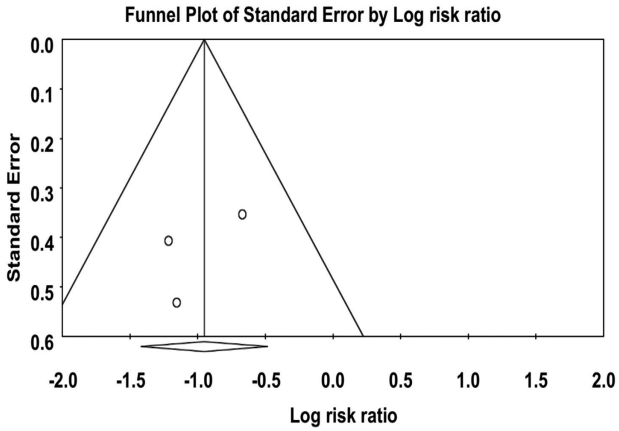

Figure A3 Funnel plot: meta-analysis for the relative risk of mortality associated with surveillance among esophageal adenocarcinoma (EAC) patients. Egger's test for funnel plot asymmetry: $P = 0.517$.