Cyclooxygenase inhibitors use is associated with reduced risk of esophageal adenocarcinoma in patients with Barrett's esophagus: a meta-analysis

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Background: Esophageal adenocarcinoma (EAC) has high mortality and is increasing in incidence. Barrett's esophagus (BE) increases the risk for EAC. Studies have reported inconsistent findings on the association between use of cyclooxygenase (COX) inhibitors and the risk of neoplastic progression in BE patients. Therefore, we performed a meta-analysis to investigate this association.

Methods: A meta-analysis was undertaken among a total of 9 observational studies using fixed- and random-effects models, comprising 5446 participants; 605 had EAC or high-grade dysplasia (HGD).

Results: Overall, COX inhibitors use was associated with a reduced risk of EAC/HGD among BE patients (relative risk (RR) = 0.64, 95% confidence interval (CI) = 0.53–0.77). Aspirin use also reduced the risk of EAC/HGD (RR = 0.63, 95% CI = 0.43–0.94), as well as non-aspirin COX inhibitors (RR = 0.50, 95% CI = 0.32–0.78). The chemopreventive effect seemed to be independent of duration response.

Conclusions: Cyclooxygenase inhibitors use is associated with a reduced risk of developing EAC in patients with BE. Both low-dose aspirin and non-aspirin COX inhibitors are associated with a reduced risk of neoplasia. More well-designed randomised controlled trials are needed to increase our understanding of the chemopreventive effect of COX inhibitors.

The incidence of esophageal adenocarcinoma (EAC) has increased dramatically over the past decades (Bollschweiler *et al*, 2001; Vizcaino *et al*, 2002). With high mortality, EAC has become the most universal histological type of esophageal cancer in western countries (Polednak, 2003; Vaughan *et al*, 2005). Barrett's esophagus (BE), defined as a premalignant condition in which

any extent of metaplastic columnar epithelium replaces the normal stratified squamous epithelium of the distal esophagus, has generally been regarded as the only established precursor lesion for EAC (Spechler *et al*, 2011). BE is a relatively common condition with an estimated prevalence of about 1–2% in the general population (Ronkainen *et al*, 2005), and ∼10–15% in patients

undergoing endoscopy for gastroesophageal reflux disease (GERD) (Sharma and Sidorenko, 2005). In patients with non-dysplastic BE, the annual incidence rate of developing EAC is estimated to be around 0.33% (Desai *et al*, 2012). However, the time course and risk factors for the progression of BE to EAC remain largely unknown.

The increasing incidence of EAC and its poor prognosis have led to a search for methods to prevent the neoplastic progression of BE. Many studies, including three meta-analyses, have supported the potential of chemoprevention with cyclooxygenase (COX) inhibitors, including aspirin, non-selective non-steroidal anti-inflammatory drugs (nsNSAIDs), and selective COX-2 inhibitors, for esophageal cancer (Corley *et al*, 2003; Abnet *et al*, 2009; Sun and Yu, 2011). Corley *et al* demonstrated a protective association between COX inhibitors use and esophageal cancer (of both histological types) and provided evidence for a dose effect. Abnet *et al* found that COX inhibitors use was inversely associated with EAC in their meta-analysis. Moreover, Sun *et al* reported that COX inhibitors reduced the risk for esophageal squamous cell carcinoma. An important limitation of these studies is the absence of information on BE states in the patients. Thus COX inhibitors could exert their antitumour effect either by reducing the risk of BE patients progressing into EAC, or by reducing the risk of BE. Since BE is the only known precancerous lesion for EAC, any cancer reducing effect for COX inhibitors should be best shown among BE patients. And chemoprevention for EAC would not be advocated on a population level. However, it could reasonably be considered in high-risk groups, such as patients with BE.

Inhibition of the COX-2 enzyme is hypothesised to be one of the mechanisms by which COX inhibitors might exert their anti-tumour effects. Increased expression of COX-2 was observed in the early development of many tumours including EAC and was also found to be associated with malignant progression of BE along the metaplasia-dysplasia-adenocarcinoma sequence (Molina *et al*, 1999; Fosslien, 2000; Shirvani *et al*, 2000; Kandil *et al*, 2001; Morris *et al*, 2001; Spechler *et al*, 2011). Substantial experimental data also suggest that COX inhibitors might be effective chemopreventive agents for patients with BE. For example, COX inhibitors, both selective and non-selective, have been found to decrease the progression of EAC in animal models of GERD or BE (Buttar *et al*, 2002; Oyama *et al*, 2005; Kim *et al*, 2007). Rofecoxib was reported to reduce cell proliferation in biopsy specimens of Barrett's epithelium taken from patients (Kaur *et al*, 2002). Thus, we suggest that COX inhibitors might have an important role in preventing BE from developing into dysplasia or adenocarcinoma.

To date, only a few epidemiological studies with inconsistent results have been carried out in patients with BE. A randomised-controlled trial (RCT) published in 2007 by Heath *et al* (2007) demonstrated that secondary chemoprevention with celecoxib did not reduce the risk of developing EAC in patients with BE. Although some meta-analyses on the chemopreventive effect of COX inhibitors in esophageal cancer with limitations have been performed (Corley *et al*, 2003; Abnet *et al*, 2009; Sun and Yu, 2011), no meta-analyses assessed the association between COX inhibitors use and progression to EAC in patients with BE. So, the protective effect of COX inhibitors on the neoplastic development in patients with BE has remained uncertain.

We therefore performed a meta-analysis of existing observational studies to investigate the association between COX inhibitors ingestion and the risk of neoplastic progression in patients with BE, following the MOOSE guidelines (Stroup *et al*, 2000). We aim to give support to a more definitive answer on whether preventive use of COX inhibitors can reduce the risk of neoplastic progression in patients with BE.

MATERIALS AND METHODS

Search strategy. We conducted a computer-assisted systematic search of MEDLINE, EMBASE, and Web of Science databases from their commencement to July 2013. We used similar search terms for MEDLINE and EMBASE (see Appendix A). Web of Science was searched mainly for abstracts of additional gastro-intestinal/oncology society meetings. The language of publications was not restricted. We also reviewed the bibliographies of relevant articles to identify additional studies that might have been missed by the database searches.

Study selection. Two of the authors (ZS and DXW) indepen-dently screened titles and abstracts of the papers to identify studies that might meet the inclusion criteria and discard those that clearly did not. Full text of studies selected for further review was retrieved and evaluated. Studies were included if they met the following criteria: (1) evaluated exposure to any type of COX inhibitors; (2) the primary outcome was clearly defined as EAC or high-grade dysplasia (HGD); (3) patients included should be definitely diagnosed as having BE in the past or at present; (4) provided odds ratios (ORs), relative risks (RRs), or hazard ratios (HRs) with confidence intervals (CIs), or original data necessary to calculate the RR.

Data extraction. All data were extracted independently and crosschecked by three of the authors (ZS, ZXQ, and HSL) according to the inclusion criteria. Discrepancies were discussed and resolved by consensus. The following data were collected from each study: the first author, publication year, the country in which the study was performed, study design, medication type, informa-tion source for exposure measurement (for example, questionnaire or pharmacy database), number of participants, OR/RR/HR with corresponding 95% CI for each category, and confounders included in each adjusted estimate (Tables 1 and 2). Also, the inclusion criteria and potential types of bias of each study were provided in Supplementary Table 1. We tried to extract the risk estimates (OR/RR/HR) from the Results section with and without adjustment for multiple confounders. However, in some studies the authors did not provide the unadjusted estimates but the primary data (number of cases and controls) necessary to calculate them. For these studies, the unadjusted RRs were calculated using the Pearson Chi-Square test with SPSS Statistics 17 (IBM Corporation, Armonk, NY, USA).

Statistical analysis. Stata Statistical Software was used for all the analyses (version 12.0; Stata Corporation, College Station, TX, USA). The measure of estimated effect of interest was the RR with 95% CI. Because the risk of EAC in patients with BE is relatively low, the RR mathematically approximates the OR in case–control studies and the HR in cohort studies. We therefore reported all results as the RR for simplicity, and summary RR estimates were calculated using RR, OR, or HR reported in each study (Greenland, 1987).

The Q and I^2 statistics were used to test statistical heterogeneity among studies (Higgins and Thompson, 2002). If the results were homogeneous, then the fixed-effects model with Mantel–Haenszel method should be used. Otherwise, the random-effects model with DerSimonian and Laird method should be used (DerSimonian and Laird, 1986; Greenland, 1994; Poole and Greenland, 1999). In this meta-analysis, we calculated summary RR estimates using both the fixed- and the random-effects model, and compared them to evaluate for potential heterogeneity.

Stratified analyses were conducted for several factors including study design, medication type (aspirin and non-aspirin COX inhibitors) and duration of COX inhibitors use to examine potential interactions.

Table 1. Study characteristics

Author/country/year of publication	No. of EAC/HGD cases/No. of participants	Definition of exposure to medications	Design	Exposure	Age at baseline, years, mean or range	Exposure source[a]	Confounders included in adjusted estimates
Tsibouris/UK/2004	114/496	⩾ 2 years	Case–control/Retrospective	COX inhibitors	73 (EAC)/68.4 (BE)	Database	a, b, c, d, e, f, i
E Bani-Hani/UK/2005	44/597	—	Case–control/Retrospective	COX inhibitors	63.4	Database	a, b, c, d, e, l, m
Vaughan/USA/2005[b]	37/350	At least once a week ⩾ 6 months	Cohort/Prospective	COX inhibitors	>30	Questionnaire	a, b, d, g, l
Gatenby/UK/2009	20 (EAC)/30 (HGD/EAC)/736	—	Cohort/Retrospective	Aspirin	64.5	Database	a, b, h
Nguyen/USA/2009	33 (HGD/EAC)/344	⩾ 1 prescription	Cohort/Retrospective	COX inhibitors	60.7	Database	a, b, e
Gaddam/USA/2010	185 (HGD/EAC)/1496	—	Cohort/Prospective	COX inhibitors	62.8	—	a, d, e, g
Nguyen/USA/2010	116/812	⩾ 1 prescription	Nested case–control/Retrospective	COX inhibitors	65.0	Database	j, k
Kastelein/The Netherlands/2011	38 (HGD/EAC)/570	nsNSAIDs > 325 mg per day, aspirin < 100 mg per day	Cohort/Prospective	COX inhibitors	60.4	Database	a, b, e, h, k
Kantor/USA/2012	45/395	—	Cohort/Prospective	COX inhibitors	>30	Questionnaire	a, b, d, k

Abbreviations: BE = Barrett's esophagus; BMI = body mass index; COX = cyclooxygenase; EAC = esophageal adenocarcinoma; HGD = high-grade dysplasia; PPI = proton pump inhibitor. a, age; b, sex; c, alcohol abuse; d, smoking history; e, BE length; f, duration of reflux; g, BMI; h, baseline histology; i, hiatus hernia; j, race; k, use of other medications, e.g., PPI and statins; l, education level; m, esophagitis, benign esophageal stricture, ulcers or *H. pylori* infection.
[a]Source of exposure data.
[b]We did not obtain this study by Vaughan in the overall meta-analysis for COX inhibitors use, but we extracted data from this study for subgroup meta-analysis considering medication type (aspirin *vs* non-aspirin COX inhibitors) and duration response (shorter duration *vs* longer duration).

Table 2. Estimates of EAC/HGD (RR/OR/HR) in patients with BE for any COX inhibitors use in each study

Author/Year	COX inhibitors use (case/control)[a]	RR/OR/HR (95% CI), any intake, adjusted	RR/OR/HR (95% CI), any intake, unadjusted
Tsibouris/2004	30 (26%)/147 (38%)	0.57 (0.36–0.91)	0.64 (0.44–0.94)
E Bani-Hani/2005	25 (57%)/304 (55%)	1.41 (0.68–2.93)	1.07 (0.60–1.90)
Gatenby/2009	5 (6%)/81 (11%)	0.90 (0.34–2.37)[b]	1.51 (0.59–3.85)
Nguyen/2009	12 (36%)/157 (50%)	0.56 (0.27–1.18)	0.51 (0.25–1.04)
Gaddam/2010	—	0.65 (0.42–0.87)	—
Nguyen/2010	57 (49%)/411 (59%)	0.60 (0.40–0.92)[c]	0.66 (0.44–0.99)
Kastelein/2011	15 (40%)/303 (57%)	0.47 (0.24–0.93)[c]	0.51 (0.27–0.99)
Kantor/2012	18 (32%)/151 (43%)	0.62 (0.34–1.10)[c]	0.68 (0.38–1.23)

Abbreviations: BE = Barrett's esophagus; CI = confidence interval; COX = cyclooxygenase; EAC = esophageal adenocarcinoma; HGD = high-grade dysplasia; HR = hazard ratio; OR = odds ratio; PPI = proton pump inhibitor; RR = relative risk.
[a]We extracted the number of patients (case/control) with dispensed COX inhibitors prescriptions, and the actual rate of COX inhibitors use (case/control) from each individual study.
[b]In the study of Gatenby *et al*, the adjusted HR estimating the relationship between the risk of EAC/HGD and aspirin use was 0.90 (0.34–2.37), and the adjusted HR using only EAC as the outcome was 1.09 (0.36–3.34).
[c]These estimates of the three studies were adjusted for use of other medications (PPIs and statins).

Qualitative assessment. So far, no scale has been universally adopted for measuring quality of observational studies. Two of the authors (ZS and ZXQ) assessed study quality independently using the 9-star Newcastle-Ottawa Scale (NOS) (Wells *et al*, 2013) (see Appendix B).

Assessment of heterogeneity. For the Q statistic, heterogeneity was considered as statistically significant if $P \leqslant 0.1$ (rather than $P < 0.05$). I^2 is the proportion of total variation contributed by between-study variation (Higgins and Thompson, 2002), and values of 25%, 50%, and 75% have been regarded as

representing low, moderate, and high heterogeneity, respectively (Higgins *et al*, 2003).

We carried out several methods to avoid potential heterogeneity as much as possible and obtain confident results. First, baseline differences between groups and the impossibility to guarantee randomisation could influence the results of observational studies. So, we used each author's reported (or calculated) RR/OR/HR with and without adjustment for variable confounders to calculate summary estimated RRs. Second, we performed a sensitivity analysis by separately omitting one study at a time to assess whether the pooled estimate has changed statistically significantly compared with the results containing all the studies. Third, a subgroup analysis was carried out by stratifying analyses with several factors including study design (cohort *vs* case–control, retrospective *vs* prospective), medication type (aspirin *vs* non-aspirin COX inhibitors), and duration of COX inhibitors use (shorter duration *vs* longer duration) (Kleinbaum *et al*, 1982; Chalmers *et al*, 1983; Gerberg and Horwitz, 1988; Schulz *et al*, 1994, 1995; Jadad *et al*, 1996; Imperiale and Birgisson, 1997).

Publication bias. Qualitative and quantitative methods were used to assess the publication bias. We visually inspected the funnel plot, and used Begg's test to calculate a correlation coefficient between the log RRs and their standard errors (Begg and Mazumdar, 1994). Publication bias was considered to be present if $P \leqslant 0.1$ (Kendall and Gibbons, 1990).

RESULTS

Study characteristics. A total of 145 potential studies were identified with the MEDLINE search. In addition, the EMBASE search yielded 579 and the Web of Science search 316 potentially relevant articles. After reviewing the titles, abstracts, and some of the full text of the studies, we selected 11 publications that met the initial inclusion criteria (Tsibouris *et al*, 2004; Bani-Hani *et al*, 2005; Vaughan *et al*, 2005; de Jonge *et al*, 2006; Gatenby *et al*, 2009; Nguyen *et al*, 2009, 2010; Gaddam *et al*, 2010; Kastelein *et al*, 2011; Beales *et al*, 2012; Kantor *et al*, 2012). The studies excluded were reduplicative, review articles, animal experiments, or those which did not report on the subject of interest. Then all the 11 papers were carefully read, and 2 of them were further excluded. In the two case–control studies, the authors compared patients with BE to

patients with EAC who did not have a clear diagnosis of BE, which could lead to loss of validity of the results (de Jonge *et al*, 2006; Beales *et al*, 2012). We did not obtain any additional relevant study through manual review of the bibliographies (Figure 1).

We analysed data from the remaining nine articles, among which one was an abstract (Gaddam *et al*, 2010). We included 2 case–control studies, 6 cohort studies, and 1 case–control study nested in a well-defined cohort, comprising 5446 participants, of whom 605 were diagnosed with EAC or HGD. Because of their characteristics, the nested case–control study was included in the cohort study group. Among them two articles were published by the same authors with the same population (the Seattle Barrett's esophagus project) (Vaughan *et al*, 2005; Kantor *et al*, 2012). We chose the more recent one published in 2012 instead of the other in 2005 when performing the meta-analysis for overall COX inhibitors use. Nevertheless, the study in 2005 provided risk estimate for medication type (aspirin and non-aspirin COX inhibitors) and duration response, while the more recent one did not. Consequently, eight studies were included in the overall meta-analysis for COX inhibitors use. Data from the article published in 2005 were only used for the subgroup analysis considering medication type and duration response (Vaughan *et al*, 2005). All the meta-analysis results were shown in Table 4.

Quality of the included studies. The studies were judged to be 6, 7, 8, or 9 points on the 9-star Newcastle-Ottawa Scale. Seven studies were considered to be of high quality (>7 points). The details of the quality assessment for each study are shown in Supplementary Table 2.

Neoplastic progression (all types of COX inhibitors). Altogether a smaller proportion of cases were prescribed COX inhibitors compared with controls (38.6% *vs* 39.7%). Patients with any exposure to any type of COX inhibitors had a significant risk reduction in developing EAC/HGD (adjusted RR = 0.64, 95% CI = 0.53–0.77, $P_{homogeneity} = 0.512$) in an overall analysis using estimates adjusted for potential confounders in each study (Figure 2A). The unadjusted RR was also calculated (unadjusted RR = 0.70, 95% CI = 0.56–0.86, $P_{homogeneity} = 0.357$).

Then, we omitted one study at a time to see whether the magnitude, statistical significance, or heterogeneity had substantially changed. However, no study markedly influenced the result of summary estimates.
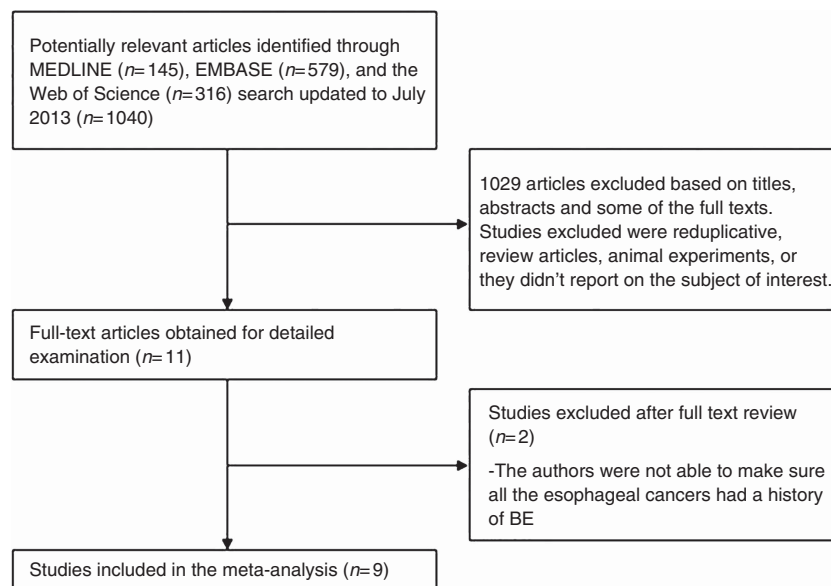

Figure 1. Flow diagram of study identification and selection.
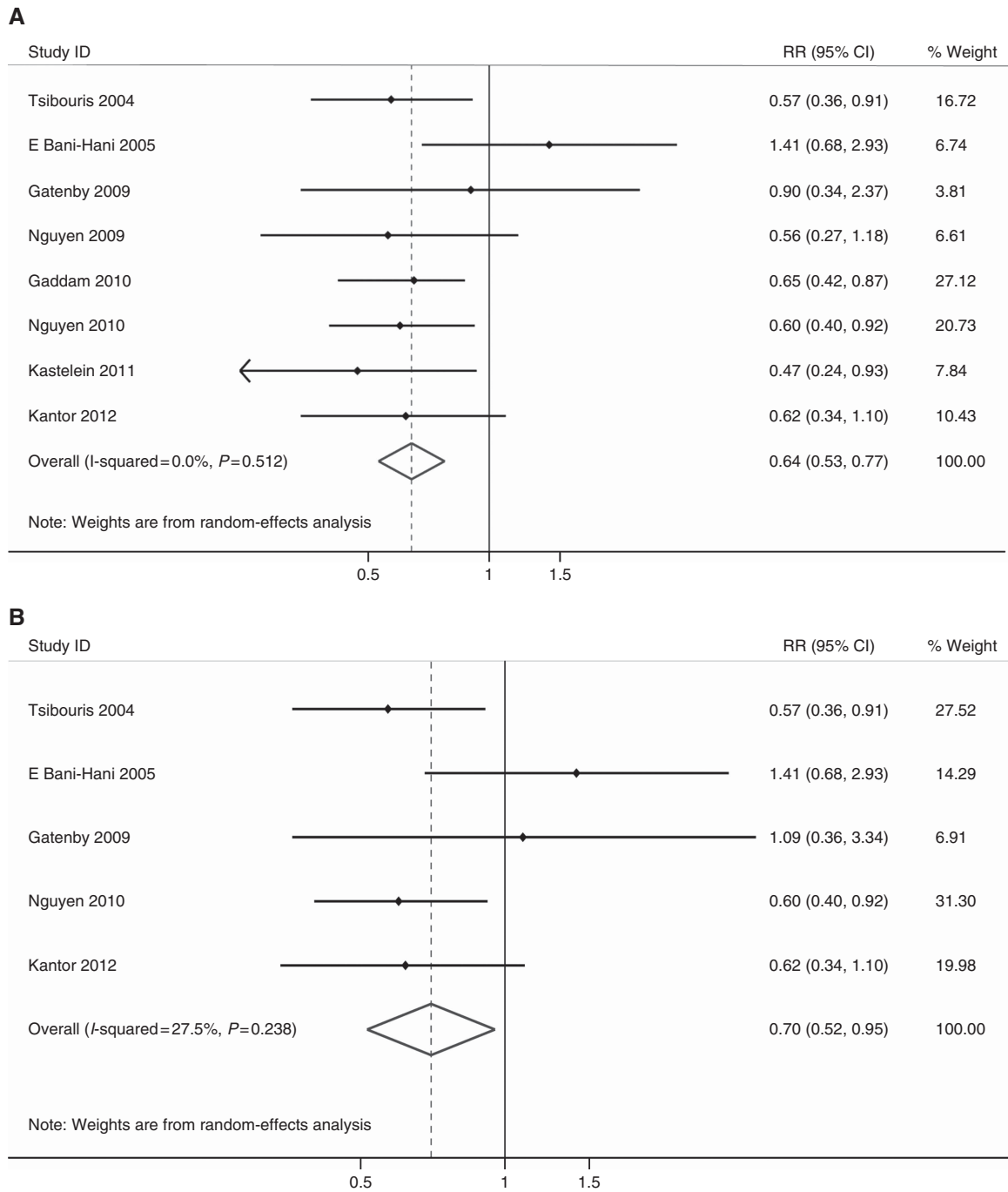
A

B

Figure 2. (**A**) Forest plot assessing overall COX inhibitors use and the risk of EAC/HGD in patients with BE. (**B**). Forest plot assessing overall COX inhibitors use and the risk of EAC only in patients with BE.

Five of the included studies used only EAC as the outcome (see Tables 1 and 2). So, we performed a subgroup meta-analysis among these studies and showed a significant risk reduction in developing EAC (adjusted RR = 0.70, 95% CI = 0.52–0.95, $P_{homogeneity} = 0.238$) (Figure 2B).

Study design. The adjusted estimates for cohort studies (adjusted RR = 0.61, 95% CI = 0.49–0.76, $P_{homogeneity} = 0.929$) were some-what different from the adjusted estimates for case–control studies (adjusted RR = 0.86, 95% CI = 0.35–2.07, $P_{homogeneity} = 0.04$) which was not statistically significant. (Figure 3).

Among the six cohort studies, three of them were retrospective and the other three were prospective. So, we performed the sensitivity analysis to investigate the difference between retrospective cohort studies (adjusted RR = 0.62, 95% CI = 0.44–0.87, $P_{homogeneity} = 0.718$) and prospective cohort studies (adjusted RR = 0.61, 95% CI = 0.46–0.81, $P_{homogeneity} = 0.709$) (see Supplementary Figure 1).

Duration response. To search for a duration response, we performed a subgroup analysis among those studies providing risk estimates for duration effect (Table 3).

Because the definition of longer duration in each study varied substantially (2 months, 1 year, 2 years, 3 years, and 5 years), we defined 1 year, 2 years, and 3 years as longer duration, and performed subgroup meta-analysis separately (see Supplementary Figure 2). Cyclooxygenase inhibitors use for >1 year was associated with a significantly lower risk of neoplastic progression
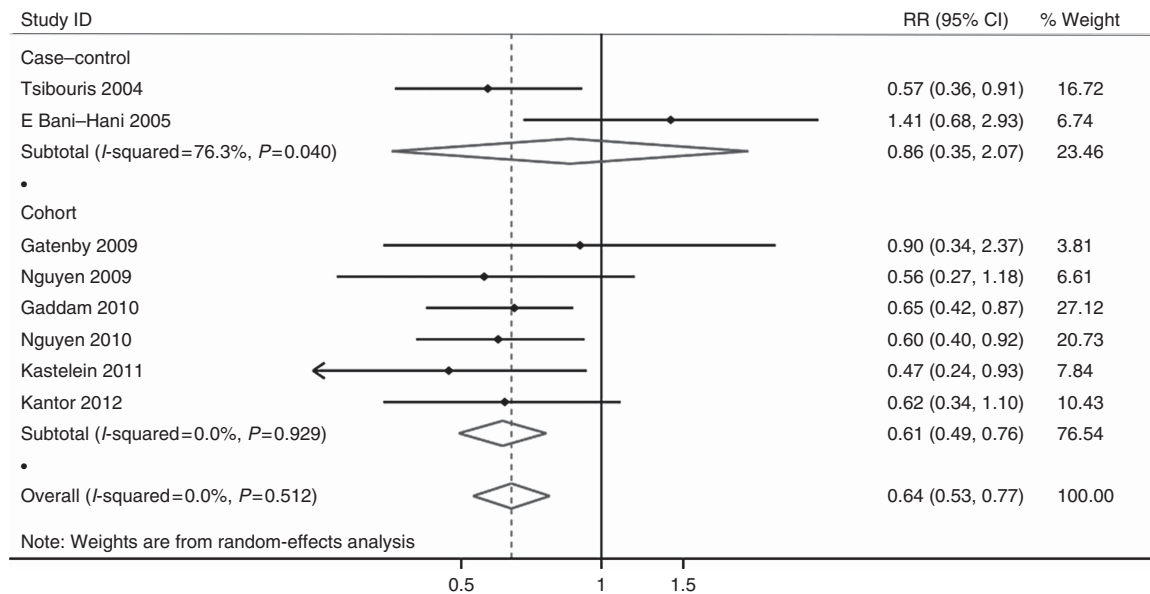
Figure 3. Forest plot of COX inhibitors intake and EAC/HGD risk in patients with BE considering study design (case–control vs cohort).

Table 3. Estimates of EAC/HGD (RR/OR/HR) in patients with BE for duration response and the numbers for cases/controls

Author/Year	Case/Control (shorter duration)	RR/OR/HR (95% CI), shorter duration, adjusted	Case/Control (longer duration)	RR/OR/HR (95% CI), longer duration, adjusted
Tsibouris/2004	—	—	14/88	0.51 (0.22–1.19) (daily use > 2 years)
Vaughan/2005	—	0.37 (0.15–0.91) (<5 years)	—	0.55 (0.25–1.21) (>5 years)
Nguyen/2009	6/80	0.49 (0.20–1.22) (<36 months)	6/59	0.53 (0.21–1.32) (>36 months)
Nguyen/2010	43/295	0.70 (0.46–1.07) (<12 months)	14/116	0.55 (0.29–1.06) (>12 months)
Kastelein/2011	10/155	0.58 (0.27–1.25) (<2 months)	5/148	0.32 (0.12–0.86) (>2 months)

Abbreviations: BE = Barrett's esophagus; CI = confidence interval; COX = cyclooxygenase; EAC = esophageal adenocarcinoma; HGD = high-grade dysplasia; HR = hazard ratio; OR = odds ratio; RR = relative risk.

(adjusted RR = 0.54, 95% CI = 0.36–0.79, $P_{homogeneity}$ = 0.999), as compared with use for <1 year (adjusted RR = 0.67, 95% CI = 0.46–0.97, $P_{homogeneity}$ = 0.674). And longer duration of COX inhibitors (>2 years) was also associated with greater risk reduction (adjusted RR = 0.53, 95% CI = 0.33–0.87, $P_{homogeneity}$ = 0.992) than shorter duration (<2 years) (adjusted RR = 0.67, 95% CI = 0.46–0.97, $P_{homogeneity}$ = 0.674). Moreover, use for >3 years was associated with a lower risk of EAC/HGD (adjusted RR = 0.54, 95% CI = 0.30–0.99, $P_{homogeneity}$ = 0.952) as compared with use for <3 years (adjusted RR = 0.64, 95% CI = 0.46–0.90, $P_{homogeneity}$ = 0.751). However, none of the differences between the three groups were statistically significant (Table 4).

Medication type. Although the study by Vaughan et al (2005) was excluded from the overall analysis for COX inhibitors use, we included it in the subgroup analysis for medication type. We extracted the risk estimates for aspirin and non-aspirin COX inhibitors use from relevant studies.

Altogether four studies provided aspirin estimates adjusted for potential confounders (Supplementary Table 3) (Tsibouris et al, 2004; Vaughan et al, 2005; Gatenby et al, 2009; Kastelein et al, 2011). Any exposure to aspirin was associated with a reduced risk of neoplastic progression (adjusted RR = 0.63, 95% CI = 0.43–0.94, $P_{homogeneity}$ = 0.642). (Figure 4).

Only three studies offered the adjusted estimate for non-aspirin COX inhibitors (Tsibouris et al, 2004; Vaughan et al, 2005; Kastelein et al, 2011). Patients with any exposure to any type of non-aspirin COX inhibitors also had a significant reduction in risk of EAC/HGD (adjusted RR = 0.50, 95% CI = 0.32–0.78, $P_{homogeneity}$ = 0.492) (Figure 4).

Concomitant use of other medications. To explore the interactive effect of concomitant use of other putative chemopreventive medications as proton pump inhibitors (PPIs) and statins, we limited analysis to studies that adjusted for use of these additional medications (Nguyen et al, 2010; Kastelein et al, 2011; Kantor et al, 2012), and compared results with those that did not adjust (Tsibouris et al, 2004; Bani-Hani et al, 2005; Gatenby et al, 2009; Nguyen et al, 2009; Gaddam et al, 2010). The results showed a 42% reduction (adjusted RR = 0.58, 95% CI = 0.43–0.78, $P_{homogeneity}$ = 0.801) for those adjusting for PPIs/statins, which was higher than those that did not adjust (RR = 0.70, 95% CI = 0.53–0.93, $P_{homogeneity}$ = 0.285), although this difference was not statistically significant ($P_{significance}$ = 0.38).

Over-the-counter medication use. Cyclooxygenase inhibitors are widely available over the counter and many studies have shown that the majority of use of these drugs is not prescribed. So, we wonder whether over-the-counter medication use will influence the overall results. In some of the included studies, information on medication use was collected prospectively, and patients also filled out a questionnaire on their use of over-the-counter medication. Besides, all information on medication use was crosschecked using pharmacy records (Kastelein et al, 2011; Kantor et al, 2012). In some other studies, the information on medication use was

Table 4. Meta-analysis results

Type of study	No. of studies (patients)	RR (95% CI) random effects	RR (95% CI) fixed effects	$P_{heterogeneity}$	$I^2_{heterogeneity}$ (%)	$P_{significance}$ between groups
All studies (adjusted)	8/5446	0.64 (0.53–0.77)	0.64 (0.53–0.77)	0.51	0	
All studies (EAC only)	5/3036	0.70 (0.52–0.95)	0.70 (0.52–0.95)	0.24	28	
All studies (unadjusted)	7/3950	0.70 (0.56–0.86)	0.69 (0.57–0.85)	0.36	7	
Study design						
Cohort studies	6/4353	0.61 (0.49–0.76)	0.61 (0.49–0.76)	0.93	0	0.41
Case–control studies	2/1093	0.86 (0.35–2.07)	0.74 (0.50–1.09)	0.04	76	
Study design in cohort studies						
Retrospective	3/1892	0.62 (0.44–0.87)	0.62 (0.44–0.87)	0.72	0	0.92
Prospective	3/2461	0.61 (0.46–0.81)	0.61 (0.46–0.81)	0.71	0	
Medication type						
Aspirin	4/2152	0.63 (0.43–0.94)	0.63 (0.43–0.94)	0.64	0	0.44
Non-aspirin COX inhibitors	3/1416	0.50 (0.32–0.78)	0.50 (0.32–0.78)	0.49	0	
Duration response						
Longer duration (>1 year)	4/2002	0.54 (0.36–0.79)	0.54 (0.36–0.79)	1.00	0	0.42
Shorter duration (<1 year)	2/1382	0.67 (0.46–0.97)	0.67 (0.46–0.97)	0.67	0	
Longer duration (>2 years)	3/1190	0.53 (0.33–0.87)	0.53 (0.33–0.87)	0.99	0	0.46
Shorter duration (<2 years)	2/1382	0.67 (0.46–0.97)	0.67 (0.46–0.97)	0.67	0	
Longer duration (>3 years)	2/694	0.54 (0.30–0.99)	0.54 (0.30–0.99)	0.95	0	0.63
Shorter duration (<3 years)	3/1726	0.64 (0.46–0.90)	0.64 (0.46–0.90)	0.75	0	

Abbreviations: CI = confidence interval; COX = cyclooxygenase; EAC = esophageal adenocarcinoma; RR = relative risk. P-values and I^2 for heterogeneity were calculated using the DerSimonian and Laird Q test. Differences between groups were considered to be statistically significant if $P_{significance} < 0.05$.
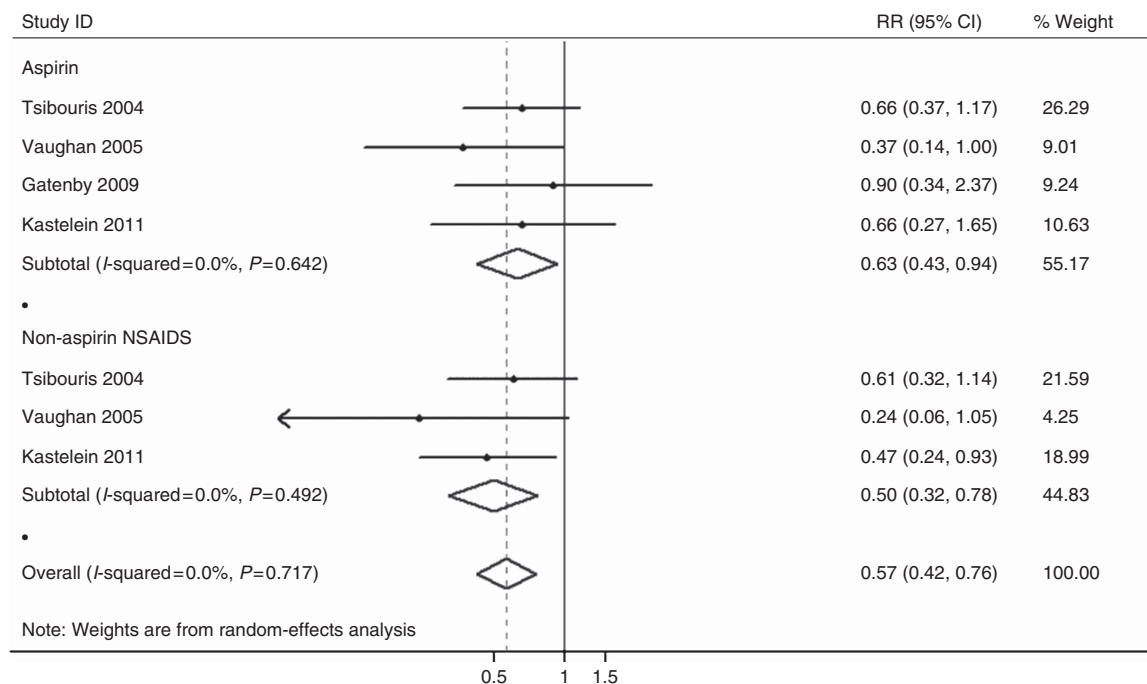

Figure 4. Forest plot of the risk of EAC/HGD associated with COX inhibitors use, organised separately by medication type (aspirin *vs* non-aspirin COX inhibitors).

collected retrospectively through questionnaires, including over-the-counter medication use (Tsibouris *et al*, 2004; Bani-Hani *et al*, 2005). Nguyen *et al* (2010) thought that patients with higher

socio-economic status might be less likely to receive COX inhibitors prescription at the Veterans Affairs pharmacy. Consequently, their multivariate analysis adjusted for the patients'

social-economic status. Nevertheless, the other included studies failed to address this problem. So, we performed a meta-analysis among the five studies including over-the counter medication use, and still found a significant risk reduction for COX inhibitors (RR = 0.64, 95% CI = 0.48–0.86, $P_{homogeneity}$ = 0.229), indicating that over-the-counter medication use might not affect the overall results.

Publication bias. As the number of the studies included in the analysis was small, visual inspection of funnel plots did not demonstrate convincing patterns. Using Begg's test to calculate a correlation coefficient between log RRs and their standard errors, we found there was no evidence of publication bias for overall summary estimates of COX inhibitors use (P = 0.902). Considering medication type, there was no obvious evidence of publication bias for aspirin or non-aspirin COX inhibitors use (P = 0.734 for aspirin, P = 0.296 for non-aspirin COX inhibitors).

DISCUSSION

In this meta-analysis, which pooled several large observational studies, a significant negative association was found between COX inhibitors use and the risk of neoplastic progression in patients with BE with an overall risk reduction of 36%. A significant risk reduction of 30% was also found for EAC development.

We observed an obvious risk reduction in cohort studies (39% reduction), while no significant risk reduction was observed in case–control studies, possibly due to recall bias and registration bias. And the number of case–control studies involved was too small to yield a convincing result. We also carried out a sensitivity analysis among the cohort studies comparing the risk estimates between retrospective (38% reduction) and prospective cohort studies (39% reduction), indicating that study design in terms of cohort studies did not affect the final results.

We also tried to explore whether there was a duration–response effect for COX inhibitors use. The classification for longer duration varied among the five studies from 2 months to 5 years. And the study of Tsibouris et al did not provide risk estimate for shorter duration (< 2 years). So, we defined longer duration as 1 year, 2 years, and 3 years, respectively, and carried out separate subgroup meta-analysis. We did not find any significant difference for risk reduction between longer duration and shorter duration, suggesting that use of COX inhibitors might be independent of duration response. In individual studies, Kastelein et al reported that NSAIDs use for > 2 months was associated with a significant trend towards a lower risk of neoplastic development than NSAIDs use for 2 months or less, and Nguyen et al demonstrated that filled COX inhibitors prescriptions for at least 12 months had a non-significant greater reduction in EAC risk than those with < 12 months' prescriptions. Nevertheless, in another study of Nguyen et al (2009), COX inhibitors use for > 3 years indicated a lower risk reduction than COX inhibitors use for < 3 years. And Vaughan et al also showed lower protective effect of COX inhibitors use for > 5 years compared with COX inhibitors use for < 5 years. With methodological limitations of meta-analysis and the varying definitions for duration response in each included study, we were not able to confirm the duration–response relationship for COX inhibitors through meta-analysis. The optimal duration of COX inhibitors use for chemoprevention in patients with BE needs to be further explored.

Only three of the included studies offered risk estimates for dose and frequency, making it difficult to draw conclusions of dose effect and frequency effect. Tsibouris et al concluded that daily use of non-aspirin COX inhibitors reduced cancer risk in patients with BE. Vaughan et al stated that most of the COX inhibitor users took one or more doses per day during regular use. But they found no relation between frequency of NSAID use and risk of esophageal

cancer (< 1 dose per day vs ⩾ 1 dose per day). Kastelein et al reported dose and frequency for nsNSAIDs (acetylsalicylic acid > 325 mg per day, carbasalate calcium > 325 mg per day), and low-dose aspirin (acetylsalicylic acid ⩽ 100 mg per day, carbasalate calcium ⩽ 100 mg per day). We could not confirm which accurate dose was associated with protective effect through meta-analysis. Corley et al suggested in their meta-analysis that both intermittent and frequent medication use were protective, with greater protection with more frequent use in the whole population, which could help us understand this problem.

When stratified by medication type, there was also a negative association between neoplastic progression and both low-dose aspirin (37% reduction) and non-aspirin COX inhibitors (50% reduction). Use of non-aspirin COX inhibitors seemed to be more effective than use of low-dose aspirin. We were not able to provide separate data for selective COX-2 inhibitors and nsNSAIDs as only one study reported the information. Kastelein et al reported use of selective COX-2 inhibitors and nsNSAIDs respectively, and concluded that only use of nsNSAIDs significantly reduced risk of EAC in patients with BE. As for individual type of COX inhibitors, Tsibouris et al stated that only diclofenac daily consumption yielded a protective effect. Additional studies are necessary to determine which type of COX inhibitors is optimal.

Chemoprevention of other medications as PPIs and statins for EAC in patients with BE has also been investigated for long, and interest in combined use of COX inhibitors and these medications has arisen recently. Among the included studies, only Kastelein et al reported that use of both COX inhibitors and statins provided a stronger risk reduction than use of COX inhibitors or statins alone. We then carried out a subgroup meta-analysis to compare the estimates of COX inhibitors use adjusting for other medications to those that did not adjust. The results indicated a non-significant greater risk reduction in neoplastic progression for concomitant use of COX inhibitors and other medications (PPIs/statins).

Although some previous epidemiological studies have confirmed the chemopreventive effect of COX inhibitors for EAC in the whole population, the absence of BE states in cases and controls might lead to a misunderstanding of how these medications could exert their antitumour effect. Our meta-analysis was the first to evaluate whether COX inhibitors can prevent patients with BE from progressing into malignancy at great length. Besides, we synthesised data on duration response and subgroups for benefit (for example, by study design and medication type), thus providing firmer summary estimates of the association.

Beales et al (2013) performed a meta-analysis of the relationship between statins use and EAC development in BE patients. They also investigated the association between COX inhibitors and the risk of EAC in BE patients among five studies, and found that use of COX inhibitors was associated with a significantly lower incidence of EAC in BE patients (OR = 0.59, 95% CI: 0.45–0.77), consistent with our results. However, they missed some original studies in their meta-analysis, and they did not provide any information on duration response or medication type.

Esophageal adenocarcinoma development experiences a long procedure through a multi-step sequence of metaplasia-dysplasia-adenocarcinoma. Cyclooxygenase inhibitors may act late or early in the pathway. Understanding that COX inhibitors could prevent BE from progressing into malignancy through our meta-analysis, we were not sure whether these medications could lower the risk of BE development in the first place. Anderson et al (2006) reported that use of aspirin and NSAIDs was associated with a reduced risk of BE (OR = 0.53, 0.31–0.90 and OR = 0.40, 0.19–0.81, respectively). Omer et al (2012) also found that current aspirin users had a lower risk for developing BE than non-users (OR = 0.56, 0.39–0.80). However, Thrift et al (2011) demonstrated that aspirin use did not reduce the risk of BE (OR = 1.16, 0.71–1.43).

Whether COX inhibitors may act at an early stage of EAC development remains to be investigated.

Our study also had some limitations. First, all included studies were observational ones, leading to lack of random allocation of the intervention compared with RCTs. Bias due to unmeasured confounding, for example, different medications use (PPIs and statins), other health problems (angiocardiopathy) and complications, could distort the results. For instance, patients with myocardial infarction use aspirin more often, and those with complications such as reflux symptoms or upper gastrointestinal ulcers might use COX inhibitors less frequently. Besides, confounders included in adjusted estimates varied significantly among these studies. Nevertheless, confounding was unlikely to fully account for the protective association of COX inhibitors. Most studies controlled for the most influential risk factors of EAC such as age, sex, smoking, and alcohol use. Some of them further adjusted for other suspected risk factors such as use of other medications (PPIs and statins), or reflux symptoms, finding that these further adjustments did not obviously change the effect estimates. For instance, one study reported an age-, sex-, and pack-years smoked-adjusted HR of 0.58 (95% CI 0.32–1.02), and found the estimate to be significantly unchanged after further adjustment for use of statins (HR 0.62 with 95% CI 0.34–1.10) (Kantor *et al*, 2012).

Second, we were not able to provide evidence for duration response. Data on detailed dose and frequency were not available in many studies, and duration for high intake of COX inhibitors was obviously different in each study, making it difficult for us to definitively draw conclusions of the accurate dose, frequency, or duration of COX inhibitors needed for a greater antitumour effect.

Third, reverse causation might exist in the included studies. To control for reverse causation in cohort studies, that is to avoid prevalent or existing cases of cancer, those patients with BE who were diagnosed as EAC during a given interval or had a follow-up of less than that given interval, ranging from 5 months to 1 year after the initial diagnosis of BE, were excluded from each individual analysis. As for case–control studies, Tsibouris *et al* stated that they removed patients who started COX inhibitors in the 4 years before the diagnosis of EAC to avoid collecting data on medication consumption caused by the underlying pathology, thereby avoiding reverse causation. Thus, we were able to keep to a minimum this possibility of reverse causation.

Fourth, we failed to address how to balance the risks and benefits of COX inhibitors through meta-analysis. The well-recognised side effects of aspirin and NSAIDs were upper gastrointestinal bleeding, peptic ulceration, and haemorrhagic stroke. Many approaches to reduce harmful effects of these medications were under investigation, including co-administration with PPIs, histamine-2 receptor antagonists, and *Helicobacter pylori* eradiation.

Additional well-designed epidemiological studies are needed to enhance our understanding of the relationship between COX inhibitors use and neoplastic development in patients with BE, especially high-quality double-blinded RCTs. Heath *et al* (2007) has published results of an RCT on behalf of the Chemoprevention for Barrett's Esophagus Trial (CBET) Research Group. The reason why we did not bring it in our meta-analysis was that the outcomes did not meet with our inclusion criteria. Disappointingly, results of the phase II b multicentre trial indicated lack of secondary chemoprevention of celecoxib in patients with Barrett's dysplasia, which contradicted our own data. The outcomes of the RCT measured change from baseline to the active treatment period (48 weeks) in the following parameters: the proportion of biopsy samples exhibiting dysplasia, the highest grade of dysplasia, the extent of HGD/low-grade dysplasia (LGD), and the surface area affected by BE. However, our meta-analysis measured the risk of neoplastic progression in patients with BE, which was totally different from the RCT. Moreover, the treatment duration was set as 48 weeks to at most 2 years in the RCT, which presumably is too short to reliably investigate the occurrence of EAC in most of the patients. And the number of patients (82) with BE included in the trial was rather small. All these contributed to the contradiction between our analysis and the RCT. However, the UK ASPECT trial utilising aspirin is in follow-up and should provide much more data soon.

In summary, our meta-analysis shows a negative association between COX inhibitors use and the risk of neoplastic progression in patients with BE. Both non-aspirin COX inhibitors and low-dose aspirin are associated with a reduced risk of neoplasia, and non-aspirin COX inhibitors seem to be more effective. However, COX inhibitors use seems to be independent of duration response. Future research should include more well-designed RCTs on the relationship between COX inhibitors use and the risk of EAC development in patients with BE.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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APPENDIX A

APPENDIX A MEDLINE search strategy
Key words and medical subject heading (Mesh) terms for the MEDLINE search included: ('Barrett Esophagus' [Mesh]) AND ('Anti-Inflammatory Agents, Non-Steroidal' [Mesh] OR 'non-steroidal anti-inflammatory drugs' OR diclofenac OR indomethacin OR aspirin OR ibuprofen OR naproxen OR ketorolac OR etodolac OR sulindac OR 'COX2-inhibitors' OR celecoxib OR rofecoxib OR valdecoxib).

APPENDIX B

APPENDIX B Description of quality score
The 9-star Newcastle-Ottawa Scale (NOS) evaluates the study quality in three categories: selection, comparability, and exposure (case–control studies) or outcome (cohort studies). The NOS assigns a maximum of four questions for selection of study groups, two questions for comparability of study groups, and three questions for ascertainment of the outcome of interest. All questions have a score of 1, except for comparability, for which separate points are awarded for controlling for age and/or sex (maximum, 2 points). Nine points on the NOS reflect the highest study quality. Any discrepancies were resolved by a joint re-evaluation of the original articles.