



# Risk of esophageal adenocarcinoma in patients with Barrett's esophagus using proton pump inhibitors: a systematic review with meta-analysis and sequential trial analysis

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**Background:** Proton pump inhibitors (PPIs) have been used to treat Barrett's esophagus (BE), but there seems to be insufficient evidence that PPIs can prevent esophageal adenocarcinoma (EAC) and high grade dysplasia (HGD). This study aimed to evaluate the effects of PPIs in BE patients.

**Methods:** PubMed and EMBASE were systematically searched. Stata13 and trial sequential analysis (TSA) software were used to carry out related statistics. Pooled odds ratio (OR) with 95% confidence intervals (CIs) were calculated.

**Results:** Using PPIs to reduce the incidence of EAC and HGD has not been confirmed (OR, 0.61; 95% CI, 0.29–1.26). The pooled results of three cohort studies reported that PPIs use was protective (OR 0.48; 95% CI, 0.33–0.70). But the pooled results of five case-control study indicating PPIs use does not prove this protective effect (OR 0.73; 95% CI, 0.21–2.48). On pooled analysis of 4 US studies 2 Netherlands, protective effect on development of EAC and HGD was noted (OR, 0.59; 95% CI, 0.43–0.80) and (OR, 0.16; 95% CI, 0.03–0.75).

**Conclusions:** According to the Meta analysis and TSA of existing studies, the protective effect of PPIs on the progression of BE patients to EAC and/or HGD has not been confirmed. TSA shows that more patients are needed before a clear conclusion can be reached.

**Keywords:** Proton pump inhibitors (PPIs); esophageal adenocarcinoma (EAC); high grade dysplasia (HGD); Barrett's esophagus (BE); meta-analysis; trial sequential analysis (TSA)

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## Introduction

The incidence of esophageal adenocarcinoma (EAC) has increased (1), with gastroesophageal reflux thought to be a major contributor to the occurrence of EAC and high grade dysplasia (HGD). Barrett's esophagus (BE) is one of the steps in which adverse events occur and is characterized by the squamous epithelium of the lower part of the esophagus

being covered by the columnar epithelium. Gastric acid can be reduced by proton pump inhibitors (PPIs), which then can slow the BE process. At present, PPIs are recommended for the treatment of BE, but the evidence concerning PPIs' use to prevent the progression from BE to HGD and EAC seems to be insufficient. Several studies have reported that using PPIs may decrease the risk of HGD and EAC (2,3).

In contrast, other studies have suggested that PPI use can increase the risk of HGD and EAC (2,4). The effects of PPIs on the risk of EAC and HGD in patients with BE thus remains controversial. Consequently, we conducted a meta-analysis and trial sequential analysis (TSA) to clarify PPI administration for EAC and HGD. We present the following article in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) reporting checklist (5) (available at <http://dx.doi.org/10.21037/tcr-20-3362>).

## Methods

### *Data sources, search strategy, and study selection*

PubMed and EMBASE were searched through September 1, 2020, with some studies being manually searched to locate further resources. The comprehensive list of search terms is displayed in [Appendix 1](#). All studies were selected by two independent reviewers (Lunan Li and Zhongsheng Cao). The articles reporting relative risk (RR) or odds ratio (OR), or that provided data for their calculations, were deemed eligible for inclusion. Conference abstracts were excluded. Inclusion in the meta-analysis was not otherwise restricted by study size or language. In cases where reviewers disagreed about the inclusion of an article, a consensus was achieved through group discussion.

### *Data extraction and quality assessment*

Data from each included study were extracted by two independent reviewers (Lunan Li and Zhongsheng Cao). The required information included the first author's name, publication year, country, age distribution, sex distribution, and research type. Any disagreements concerning the data to be extracted were resolved through discussion to maintain consistent results. Each article's quality was independently assessed by two reviewers (Lunan Li and Zhongsheng Cao) using the Newcastle–Ottawa scale (NOS) (6,7). Any discrepancies in the quality assessment were resolved via group discussion.

### *Data analysis*

Stata 13 (StataCorp, College Station, TX, USA) was used for statistical analyses. TSA program version 0.9 beta was used to control random errors and evaluate inaccuracies. The heterogeneity was calculated with  $I^2$  statistic and valued

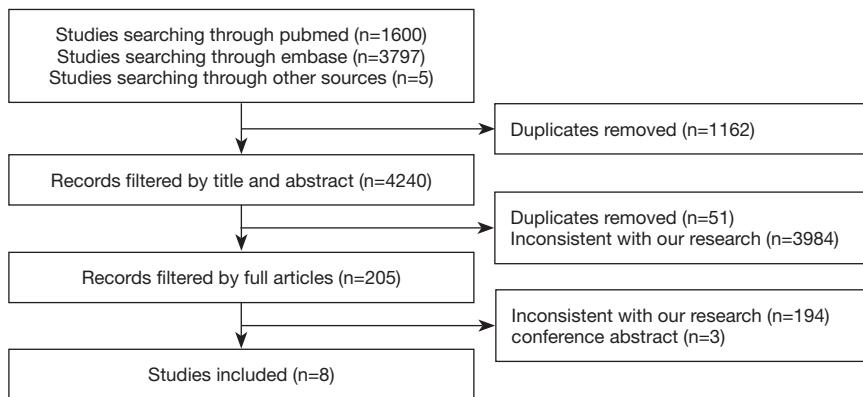
greater than 75%, indicating considerable heterogeneity (8). When heterogeneity was present, the random-effects model, as DerSimonian and Laird described, was used to calculate ORs and 95% confidence intervals (CIs) (9). Subgroup analyses were conducted to evaluate results across different study types and countries. TSA was used to estimate the amount of information needed for the meta-analysis of conclusions and to evaluate whether or not the results had type I errors due to an insufficient number of studies included. There is a risk of random errors in a conventional meta-analysis that can arise from sparse data and repeated tests (10). The TSA depends on the quantification of the amount of information required. The random-effects model was used for our study. We calculated the OR with 95% CI for each included trial. Using TSA was to keep the overall risk of type I errors at 5% and the power at 80%. To calculate the required information size, we used 11% of the event incidence in the control group for meta-analysis.

## Results

The study selection process is shown in *Figure 1*. A total of 8 studies (3 cohort studies and 5 case-control studies) comprising 7,053 patients were included (2,11–17). The characteristics of each study are presented in *Table 1*. The quality of the methodology included in the study ranged from medium to high (*Table 2*).

The meta-analysis of the 8 studies of BE patients did not completely confirm the use of PPIs to reduce the incidence of EAC and HGD (OR, 0.61; 95% CI, 0.29–1.26) and showed significant heterogeneity ( $I^2=89.7\%$ ; *Figure 2*). Studies examining the association between PPIs and the progression of EAC or HGD in BE patients were inconsistent in study design and study location. In 3 cohort studies that reported the risk of BE patient progression to HGD and EAC, PPI use was shown to be protective (OR, 0.48; 95% CI, 0.33–0.70;  $I^2=0.0\%$ ; *Figure 3*). However, the 5 case-control studies, which comprised 5144 BE patients, did not confirm that PPI use has a protective effect (OR, 0.73; 95% CI, 0.21–2.48), with considerable heterogeneity being present across studies ( $I^2=94.0\%$ ) (*Figure 3*). The pooled analysis of 4 studies in a US subgroup suggested a protective effect against the development of EAC and HGD (OR, 0.59; 95% CI, 0.43–0.80;  $I^2=3.2\%$ ; *Figure 4*). Another subgroup consisted of 2 studies from the Netherlands that assessed PPI's effect on the development of EAC and HGD in BE (OR, 0.16; 95% CI, 0.03–0.75;  $I^2=90.2\%$ ; *Figure 4*).

TSA (*Figure 5*) showed that the trial monitoring

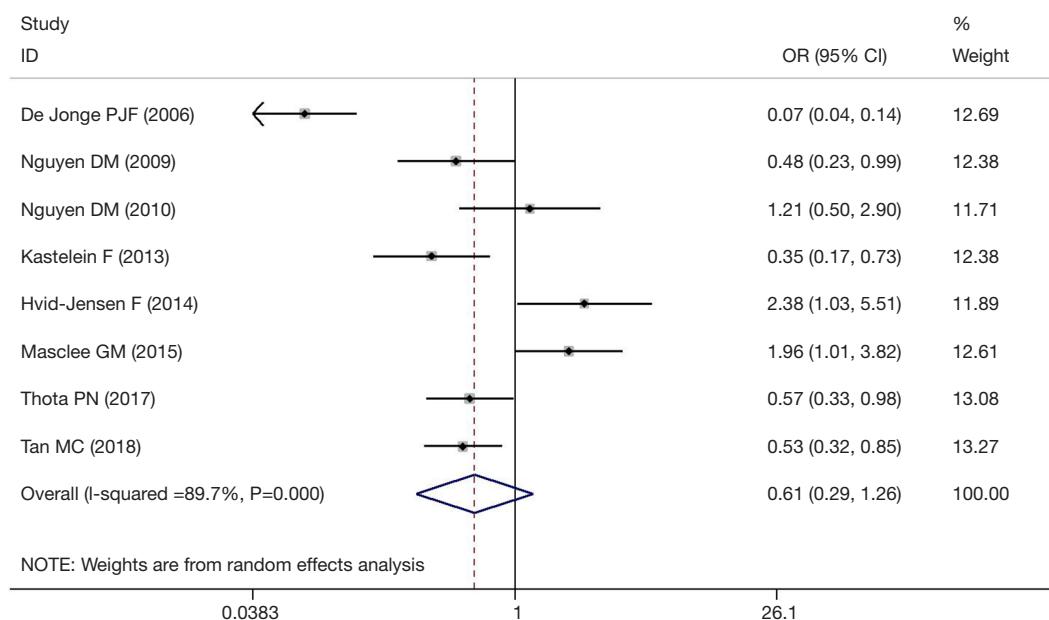
**Figure 1** Flow diagram.**Table 1** Characteristics of studies included in meta-analysis and trial sequential analysis

Author	Year	Country	Patients on PPI (n=5,762)		Patients not on PPI (n=1,291)		Research type
			EAC and/or HGD	Total	EAC and/or HGD	Total	
de Jonge PJ	2006	Netherlands	43	270	44	61	Case-control study
Nguyen DM	2009	America	17	231	16	113	Cohort study
Nguyen DM	2010	America	110	763	6	49	Case-control study
Kastelein F	2013	Netherlands	28	462	12	78	Cohort study
Hvid-Jensen F	2014	Denmark	134	1,306	6	131	Case-control study
Mascllee GM	2015	UK and Netherlands	46	1,005	11	461	Case-control study
Thota PN	2017	America	32	701	25	324	Cohort study
Tan MC	2018	America	270	1,024	30	74	Case-control study

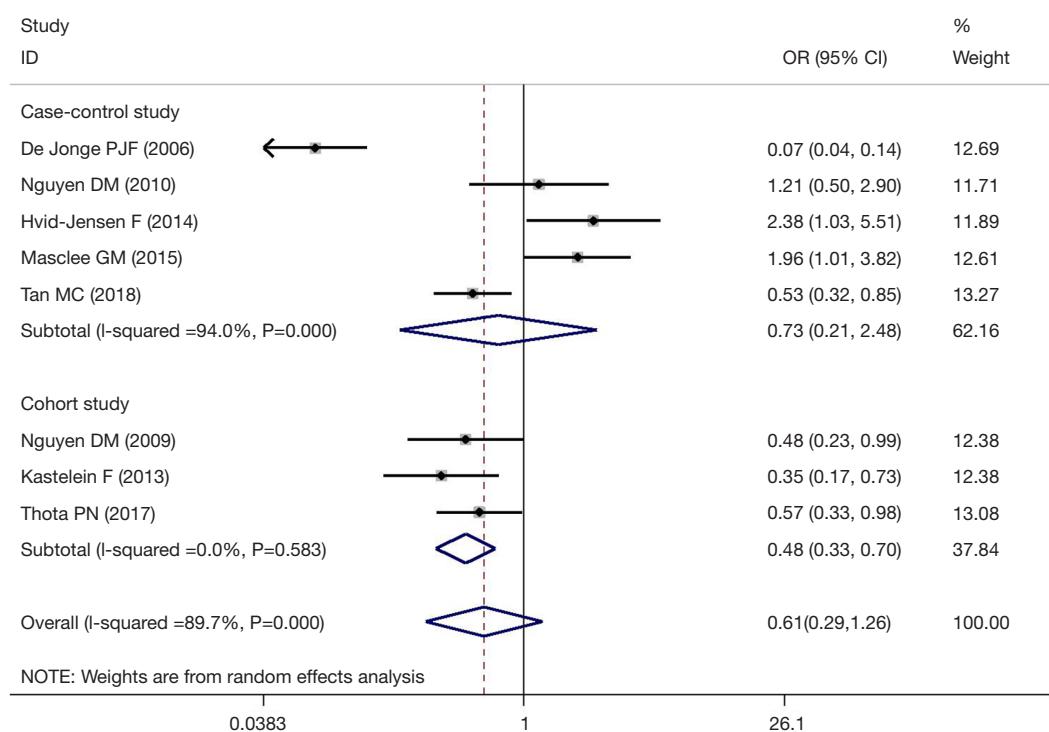
PPIs, Proton pump inhibitors; EAC, Esophageal adenocarcinoma; HGD, High grade dysplasia.

**Table 2** Quality assessment of studies included in meta-analysis and trial sequential analysis

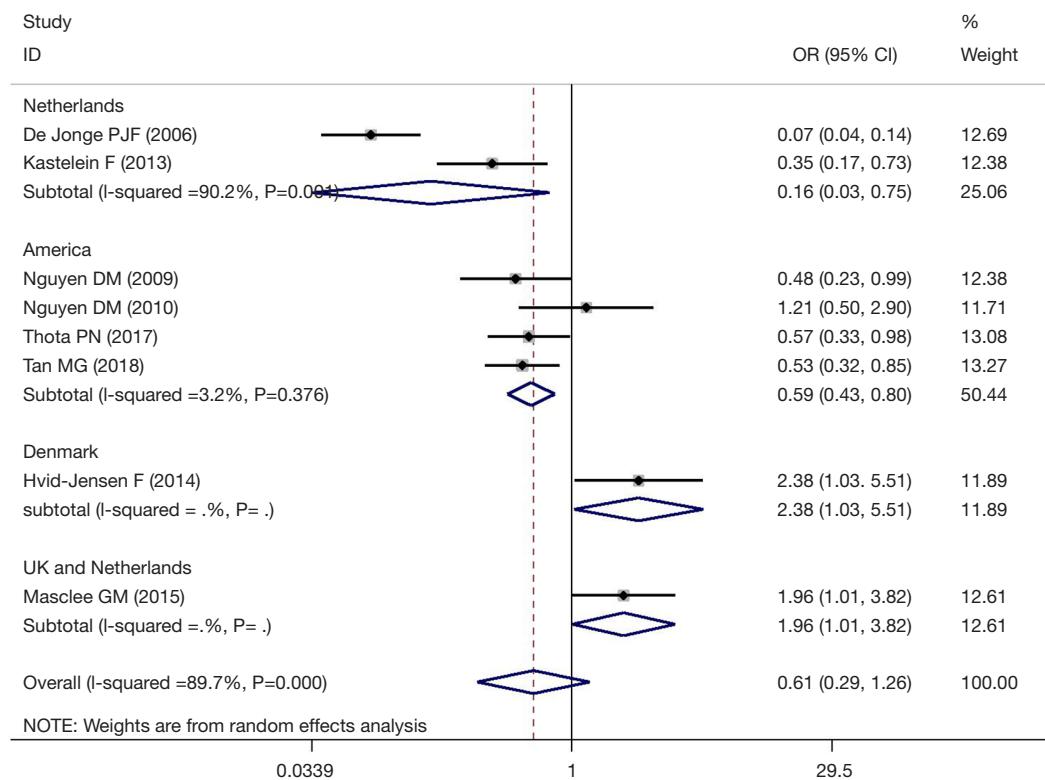
Study	Year	Study quality (NOS)			
		Selection	Comparability	Outcome/Exposure	Overall quality score (maximum 9)
de Jonge PJ	2006	***	**	**	7
Nguyen DM	2009	****	**	***	9
Nguyen DM	2010	****	**	**	8
Kastelein F	2013	****	**	***	9
Hvid-Jensen F	2014	****	**	***	9
Mascllee GM	2015	****	**	***	9
Thota PN	2017	***	**	***	8
Tan MC	2018	****	**	**	8



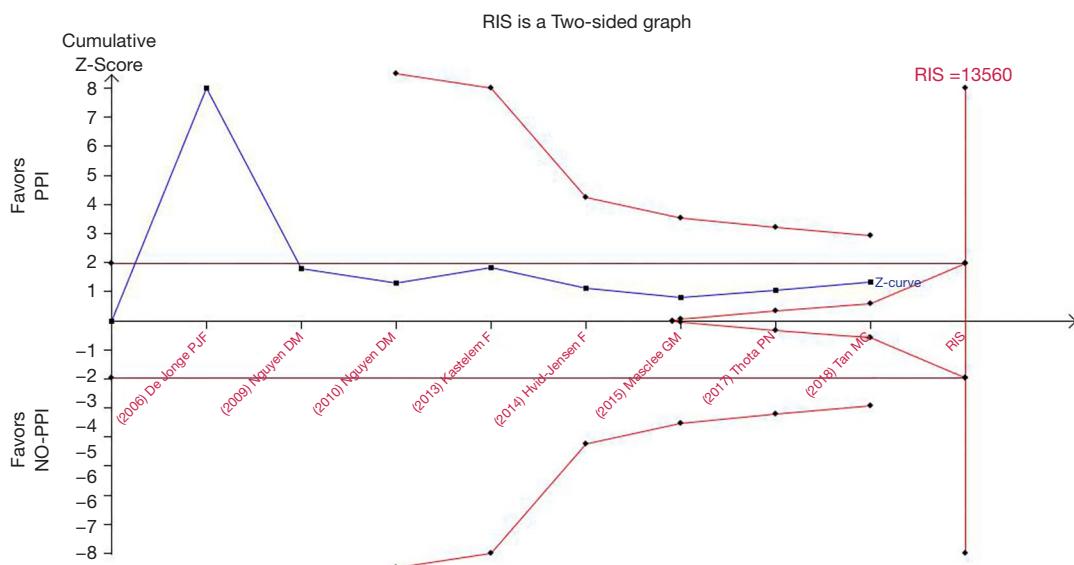
**Figure 2** Pooled of the risk of EAC and/or HGD in patients with BE with PPIs exposure in included studies. EAC, esophageal adenocarcinoma; HGD, high grade dysplasia; BE, Barrett's esophagus; PPIs, Proton pump inhibitors.



**Figure 3** Subgroup analysis of the risk of patients EAC and/or HGD in patients with BE. EAC, esophageal adenocarcinoma; HGD, high grade dysplasia; BE, Barrett's esophagus.



**Figure 4** Subgroup analysis of the risk of patients EAC and/or HGD in patients with BE. EAC, esophageal adenocarcinoma; HGD, High grade dysplasia; BE, Barrett's esophagus.



**Figure 5** Trial Sequential Analysis of PPIs use and risk of EAC and/or HGD in patients with BE. EAC, esophageal adenocarcinoma; HGD, high grade dysplasia; BE, Barrett's esophagus; PPIs, Proton pump inhibitors; RIS, required information size.

boundary for benefit was not crossed. The TSA of all trials showed that the amount of information accumulated was far from the amount of information needed and that more than 13,560 patients might be needed to draw firm conclusions. The overall pooled results showed no statistical difference (random-effects model: OR, 0.61; 95% CI, 0.29–1.26).

## Discussion

In a meta-analysis of 7,053 patients, PPIs' use to reduce the risk of HGD or EAC in BE was not confirmed, with significant heterogeneity being present. Our results are consistent with previous systematic assessments (18). Our analysis included additional procedures to provide a more reliable and comprehensive estimate of EC risk. With the increase in the number of participants, TSA was conducted to evaluate the statistical results' statistical value and guide further research.

BE is one of the complications of gastroesophageal reflux disease (GERD). Therefore, a reduction in gastric acid is generally the main strategy for treating patients with BE. Acid exposure has also been shown to upregulate the expression of cyclooxygenase-2 (COX-2) in BE (acid). COX-2 expression is increased during the early development of many tumors, including EAC, and is closely related to BE's development into EAC (19,20). One meta-analysis showed that the use of COX inhibitors was negatively correlated with the risk of tumor progression in patients with BE (21), but these inhibitors' protective effect remains controversial. Other analyses have found contradictory results regarding the use of H2 receptor antagonists (H2RA) and the development of HGD or EAC, with some even reporting an increase in the risk of HGD or EAC (4,22). Bile exposure has also been shown to upregulate the expression of COX-2 in BE (23). Interestingly, PPIs' main preventive mechanism is to promote the healing of esophageal mucosa by reducing esophageal acid and bile exposure.

Our meta-analysis did not find definite evidence supporting PPI intervention for improving the incidence of EAC in patients with BE. The results of our cohort study were different from those of our case-control study. One potential explanation for this result is the immortal time bias (24), which can produce illusory evidence for a therapeutic effect in some cohort studies.

PPIs have been shown to improve GERD in patients (25); however, whether or not the treatment of BE with PPIs reduces cancer risk remains unclear. Several randomized

controlled trials have found that endoscopic therapy can effectively eliminate dysplasia and metaplastic epithelium, greatly reducing cancer incidence. Many treatments for BE, such as radiofrequency ablation, argon plasma coagulation, photodynamic therapy, endoscopic mucosal resection, and others have been applied. The presence of nodules, ulcers, or strictures in BE is thought to be associated with an increased risk of EAC (26). Once it occurs, patients' adverse effects may be minimized by removing the lesion rather than administering medication.

A few limitations to our study should be addressed. First, PPI dose effects, the timing of PPI use, and the occurrence of adverse events were not examined. Second, due to the limited number of studies analyzed, publication bias assessment was not conducted (27). However, we did conduct TSA to intuitively demonstrate that the treatment of BE by PPIs is still controversial and requires further exploration.

## Conclusions

A meta-analysis and TSA of existing studies found no definitive evidence for PPIs' protective effect on the progression of BE patients to EAC or HGD. Indeed, the TSA suggests that more patients need to be included in the study before a clear conclusion can be reached.

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## Footnote

**Reporting Checklist:** The authors have completed the PRISMA reporting checklist. Available at <http://dx.doi.org/10.21037/tcr-20-3362>

**Conflicts of Interest:** All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr-20-3362>). The authors have no conflicts of interest to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved.

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