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Antireflux surgery and risk of esophageal adenocarcinoma : a systematic review and meta-analysis

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Title: Antireflux surgery and risk of esophageal adenocarcinoma: A systematic review and meta-analysis

Short title: Antireflux surgery and esophageal cancer

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Abbreviations:

EAC: Esophageal adenocarcinoma

GERD: Gastroesophageal reflux disease

IRR: Incidence rate ratio

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Author contributions:

JMO: acquisition of data, analysis and interpretation of data, drafting of the manuscript

PK: analysis and interpretation of data, statistical analysis

JL: study concept and design, critical revision of the manuscript for important intellectual content, obtained funding, study supervision

NB: study concept and design, acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, obtained funding, study supervision

Abstract

Objective: To investigate the preventive effect of antireflux surgery against esophageal adenocarcinoma (EAC), compared to medical treatment of gastroesophageal reflux disease (GERD) and to the background population.

Background: GERD is causally associated with EAC. Effective symptomatic treatment can be achieved with medication and antireflux surgery, yet the possible preventive effect on EAC development remains unclear.

Methods: This systematic review identified 10 studies comparing EAC risk following antireflux surgery with non-operated GERD patients, including 7 studies of patients with Barrett's esophagus; and 2 studies comparing EAC risk after antireflux surgery to the background population. A fixed-effects Poisson meta-analysis was conducted to calculate pooled incidence rate ratios (IRR) and 95% confidence intervals (CI).

Results: The pooled IRR in patients following antireflux surgery was 0.76 (95% CI 0.42-1.39) compared to medically treated GERD patients. In patients with Barrett's esophagus, the corresponding IRR was 0.46 (95% CI 0.20-1.08), and 0.26 (95% CI 0.09-0.79) when restricted to publications after 2000. There was no difference in EAC risk between antireflux surgery and medical treatment in GERD patients without known Barrett's esophagus (IRR 0.98, 95% CI 0.72-1.33). The EAC risk remained elevated in patients following antireflux surgery compared to the background population (IRR 10.78, 95% CI 8.48-13.71). While the clinical heterogeneity of the included studies was high, the statistical heterogeneity was low.

Conclusions: Antireflux surgery may prevent EAC better than medical therapy in patients with Barrett's esophagus. The EAC risk following antireflux surgery does not seem to revert to that of the background population.

Keywords: Neoplasm; cancer; gastroesophageal reflux; prevention; incidence.

Introduction

Gastroesophageal reflux disease (GERD) is a strong and dose-dependent risk factor for esophageal adenocarcinoma (EAC).[1, 2] The incidence of EAC has increased rapidly in the Western world during the last 4 decades, and the prognosis has remained poor (<15% survival in Western societies).[3, 4] Thus, preventive measures are highly warranted. Antireflux therapy might be one such measure, but the available literature is limited and has failed to establish any conclusive preventive effects against EAC. The main treatment options for severe GERD are medical (mainly proton pump inhibitors or H2 receptor antagonists) or surgical (various types of fundoplication).[5-7] Two previous meta-analyses of patients with GERD and Barrett's esophagus found no preventive effect of antireflux surgery in the development of EAC compared to medical treatment.[8, 9] However, both these meta-analyses included studies evaluating only one treatment and pooled the medically treated patients in one group and the surgically treated patients in another. This could lead to methodological difficulties when comparing any preventive effects.[8, 9] A third, more recent meta-analysis concluded that antireflux surgery does not prevent EAC in patients with Barrett's esophagus based on a high postoperative tumor progression rate.[10] The first objective of the present study was to perform a systematic review and meta-analysis comparing the risk of EAC in patients following antireflux surgery compared to medically treated patients with GERD, with or without Barrett's esophagus, and only include studies with both treatment arms. The second objective was to assess the risk of EAC following antireflux surgery compared to the risk of EAC in the corresponding background population.

Methods

Study design

A systematic literature review and meta-analysis was performed, which followed an a-priori established study protocol. The results are reported in accordance with the PRISMA ('Preferred Reporting Items for Systematic Reviews and Meta-Analysis') guidelines.[11] The search aimed to identify all studies addressing the risk of EAC following antireflux surgery compared to medication in patients with GERD, with and without Barrett's esophagus, or compared to the background population. All definitions of GERD and antireflux surgery were considered eligible for inclusion and no language restriction was applied. The time period was from an unbounded start date to June 12, 2014. Three scientific search engines were used: PubMed/MedLine database, Web of Science, and Cochrane. To identify relevant studies, the following search terms were used: esophageal, esophagus, neoplasm, adenocarcinoma, cancer, Barrett, fundoplication, antireflux surgery, Nissen, and reflux surgery (taking into account different spellings). Backward and forward citation tracking of the identified studies was performed by screening reference and citation lists in the Web of Science to identify potential additional articles. The selection of relevant articles was performed by two investigators separately (JMO and NB) after which all selected articles were compared. The final assessment of the eligibility of the articles remaining after exclusion of irrelevant articles was performed by all authors.

Study selection

Studies were included if they provided original data on the incidence of EAC in patients with GERD undergoing surgical treatment compared to medically treated patients with GERD (with or without Barrett´s esophagus) or the corresponding

general background population. To increase statistical power, no restrictions were made regarding type of antireflux medication or antireflux surgery procedure. To be included, the study needed to have reported the type of intervention performed in each comparison group, the incidence of EAC in each group, and the total follow-up time (reported or deductible) to enable calculation of incidence rates. Any patients developing high-grade dysplasia were included in the EAC group. To be eligible for inclusion, there had to be at least 1 reported case of EAC in one or both of the comparison groups. Eligible studies included cohort studies, case-control studies and intervention studies (randomized clinical trials), and both prospective and retrospective studies. Case reports, case series, cross-sectional studies and non-original articles (e.g. reviews, editorials and comments) were excluded, as were animal studies and those without a comparison group. A quality assessment of the included articles was based on the methods of selecting study participants, methods for measuring the exposure and outcome, sources of bias, methods for controlling for potential confounding, and conflicts of interests.[12]

Data synthesis and statistical analysis

The total number of person-years of the comparison groups were either calculated or extracted from the selected articles. The meta-analysis was conducted using the R package metaphor.[13, 14] A fixed-effects Poisson meta-analysis was used to calculate the pooled incidence rate ratio (IRR) and 95% confidence intervals (CI).[15] The IRR was considered statistically significant if the 95% CI did not include the number 1, which corresponds with no effect. In the statistical model, the studies were weighted due to the size of the cohorts. A random effects Poisson meta-analysis showed similar results as the fixed-effects Poisson meta-analysis. The included studies were separated

into two groups: 1) Antireflux surgery compared to a medicated GERD population with and without Barrett's esophagus, and 2) antireflux surgery compared to the corresponding background population. In studies where one of the treatment arms had no cases of EAC, we added 0.5 to both treatment arms, an established method described in detail elsewhere.[15] In the 2 included studies using the background population as a comparison group, no follow-up time was stated for the background population. For one study, the total incidence of EAC for the background population was stated, while for the other study this information was retrieved from the authors who kindly provided additional data on the background population. Using the incidence and the incidence rate, a total follow-up time could be calculated.[16, 17] Statistical heterogeneity was assessed by means of an I^2-test and was categorized into low (<50%), moderate (51-75%), or high (>75%) according to pre-defined criteria.[18]

Results

Included studies

Among a total of 1,987 unique articles that were considered, 12 met the inclusion criteria (Figure 1). These included 7 cohort studies comparing EAC risk in patients after antireflux surgery with a medically treated GERD population,[19-25] 1 cohort study comparing EAC risk in patients following antireflux surgery without specified treatment in a GERD population,[26] 2 randomized clinical trials comparing EAC risk in patients after antireflux surgery with medicated GERD patients,[27, 28] and 2 population-based studies comparing EAC risk in GERD patients undergoing antireflux surgery to the background population.[16, 17] Of the 10 studies with non-operated GERD patients as a control group, 7 included patients with Barrett's esophagus.[19-22, 24, 25, 28] The mean follow-up time varied across studies, ranging from 1.4 years to 10.6 years (up to 42 years). The clinical heterogeneity in the included studies was large as indicated in the quality assessment presented in Figure 2.

Definitions

GERD and antireflux surgery were identified based on the International Classification of Diseases (ICD) versions 7-10 in 3 studies,[17, 23, 26] while 1 study used the American Joint Committee of Cancer (AJCC) criteria for these variables.[16] The 7 studies of Barrett's esophagus were all based on endoscopic and pathologic evaluation.[19-22, 24, 25, 28] Nissen fundoplication (360 degree wrap of the stomach around the esophagus) was the most frequently used surgical procedure. In the medication groups, proton pump inhibitors or H2-receptor antagonists were typically used, although 3 studies did not specify the type of medication (Table 1).

Antireflux surgery patients versus non-operated patients with GERD or Barrett´s esophagus

The 10 studies in this category were performed in the United States, Spain, Sweden, Ireland and the United Kingdom, and included a total of 100,479 person-years in patients following antireflux surgery and 403,459 person-years in non-operated GERD patients (Table 1). None of the individual studies showed any statistically significant differences in risk of EAC between patients after antireflux surgery and medically treated GERD patients, but the IRRs of EAC were generally lower in the antireflux surgery groups (Figure 3). The meta-analysis of all 10 studies revealed a pooled IRR of EAC of 0.89 (95% CI 0.66-1.19, I^2 0%) comparing fundoplication with no fundoplication (Figure 3). After excluding the one study comparing patients after antireflux surgery with a GERD population without known treatment, the corresponding pooled IRR decreased (IRR 0.76, 95% CI 0.42-1.39, I^2 0%). The analysis of the 7 studies of patients with Barrett's esophagus showed a decreased pooled IRR of EAC in the antireflux surgery group compared to the medically treated group (IRR 0.46, 95% CI 0.20-1.08, I^2 0%). The sub-analysis restricted to the 4 studies of Barrett's esophagus published after the year 2000 showed a further decreased risk of EAC following antireflux surgery compared to medication (IRR 0.26, 95% CI 0.09-0.79, I^2 0%), which reached the threshold of statistical significance. An analysis of 3 studies investigating GERD patients without confirmed Barrett's esophagus showed no difference in EAC risk between antireflux surgery and medical treatment (IRR 0.98, 95% CI 0.72-1.33, I^2 0%). The statistical heterogeneity in all analyses was low (I^2= 0%). Subgroup analyses by different types of medication, surgical techniques, or study designs were not feasible due to the limited number of studies meeting the inclusion criteria.

Antireflux surgery patients versus background population

Two nationwide and population-based cohort studies, from Sweden and Finland, compared the risk of developing EAC in patients following antireflux surgery to that of the background population after adjustment for age, sex and calendar period.[16, 17] The maximum follow-up times were 42 years and 26 years, in the Swedish and Finnish studies, respectively. Combining these 2 studies, the total number of person-years of follow-up was 254,952 and 166,060,651 in the antireflux surgery group and in the background population, respectively. Both studies showed a strongly increased relative risk of EAC following antireflux surgery that remained increased with longer time after surgery, and the meta-analysis revealed a pooled standardized IRR of 10.78 (95% CI 8.48-13.71, I^2 0%) (Figure 4).

Discussion

This meta-analysis provided some evidence of a decreased risk of EAC in patients following antireflux surgery compared to medicated patients with Barrett's esophagus, but not in GERD patients without Barrett's. The risk of EAC remained elevated in patients after antireflux surgery compared to that of the general background population.

A methodological advantage of this study is that it included only studies with two separate treatment arms, instead of including multiple studies with only one treatment arm. This makes comparisons more reliable, since potential confounding is to some extent taken into account due to a similar clinical setting in the comparison groups. Weaknesses include the fact that none of the included studies adjusted for duration or severity of GERD. However, the comparison groups should have been well balanced regarding confounders in the 2 intervention studies due to randomization. The statistical heterogeneity was low (I^2 was 0% in all analyses). However, there was a large clinical heterogeneity, since the study characteristics varied considerably. As with any meta-analysis, we cannot exclude the possibility that studies were missed during our search, or that studies that observed null effects were never published (publication bias). Potential influence related to changes in surgical treatment, prescription patterns of GERD medication, or duration of follow-up could not be assessed due to the lack of such data. In the clinical setting, there might have been selection bias in the decision-making, since clinicians might be more prone to recommend antireflux surgery to patients with more severe GERD and therefore an inherently higher risk of EAC. However, such bias would underestimate any protective effect of antireflux surgery against EAC and not contribute to the decreased

risk compared to medication, indicated in the present study. Another possible limitation is that different definitions for the exposure and outcome were pooled together, but again, such misclassification would dilute effects rather than cause them, and could thus lead to an underestimation of the decreased IRRs following antireflux surgery. Finally, the low number of studies and the typically small sample size and limited follow-up time in the included studies lowered the statistical power and increased the risk of chance errors. The confidence intervals were wide and even strongly decreased risk estimates were not always statistically significant.

In relation to previous meta-analyses on the subject, our meta-analysis had more strict inclusion criteria and used different methodology. One meta-analysis only reported the incidence of EAC in patients with Barrett's esophagus following antireflux surgery and medication separately, as 3.8/1000 person-years and 5.3/1000 person-years, respectively, concluding that no difference was found.[8] However, the equivalent of this risk ratio was in fact 0.72 (calculated by us). Moreover, 24 of the 34 articles included in that study had only one treatment arm. In a more recent meta-analysis that compared the risk of EAC after antireflux surgery with medication in patients with Barrett's esophagus, 20 of 25 included articles had one treatment arm only.[9] The incidence rate after surgery was 2.8/1000 person-years and 6.3/1000 person-years after medical treatment.[9] This is equivalent to a risk ratio as low as 0.44 (calculated by us). In the most recent meta-analysis, published in 2008, 35 articles examining the risk of EAC in operated patients without any comparison group concluded that antireflux surgery does not prevent EAC based on a tumor progression rate of 3.8% during a mean follow-up time of 57 months.[10]

Except for the decreased pooled risk estimates of EAC in patients following antireflux surgery compared to medication in patients with Barrett's esophagus, another argument in favor of a protective effect of antireflux surgery against EAC is that the recent studies all showed an effect size in the same direction. Yet, to establish whether any preventive effect against EAC is better following antireflux surgery than medication, there is a need for larger studies with long follow-up and adjustment for confounders that take duration and severity of GERD into account. As mentioned above, there is a risk of selection bias in the included studies. Such a bias would likely be more prone towards recommending surgery to patients with more severe GERD who are at higher risk of EAC at baseline, and this might lead to an underestimation of the possible preventive effect of surgery compared to medication. Since this would lead to an underestimation of the effect in the meta-analysis as well, the chance of a stronger preventive effect following antireflux surgery cannot be excluded based on the available data.

Although medication came out as being less effective than antireflux surgery in preventing EAC, this study cannot exclude a preventive effect of medication. While individual studies have mostly failed to detect any preventive effect of medication against EAC, a recent meta-analysis found a pooled odds ratio as low as 0.29 (95% CI 0.12-0.79) comparing patients on PPI with unspecified non PPI-users.[29]

The reasons for the potentially stronger preventive role of antireflux surgery for EAC compared to medication include the fact that antireflux surgery creates a mechanical barrier against all contents included in the refluxed juice, including duodeno-gastroesophageal reflux of bile and pancreatic juice, which could be particularly

harmful from a carcinogenic point of view.[30] Medical treatment does not prevent such reflux per se, but mainly decreases the acidity of the refluxate. Moreover, a recent 5-year follow-up of a randomized clinical trial using pH-measurements showed a lower level of pathologic acidity in the esophagus after surgery compared to medication in GERD patients.[31] Finally, compared to medication, fundoplication is not dependent on dosage or compliance.

In this study, the risk of developing EAC remained elevated in patients undergoing antireflux surgery compared to that of the background population. This could be explained by a particularly high severity of GERD in patients selected for antireflux surgery, where the DNA is already damaged, leaving the operated patients at a long-term increased risk of EAC compared to the population at large. Moreover, the prevalence of Barrett's esophagus is certainly higher in the antireflux surgery group than in the general population, and the Barrett's mucosa does not disappear despite effective treatment of GERD. Furthermore, some of the patients undergoing antireflux surgery will have recurrence of GERD, again increasing the risk of EAC compared to the background population.[23, 32, 33] Although, it might be that a reduction of the risk to that of the background population is not a reasonable goal due to the fact that many patients already have a premalignant condition. However, this is seldom the goal of other disease preventive measurements, where the aim usually is a risk reduction compared to alternative therapies or no treatment, rather than a reduction to the level of the background population.

This meta-analysis suggests that antireflux surgery could be beneficial for patients with Barrett's esophagus from a cancer preventive perspective, although uncertainty

remains. A recent Cochrane review concluded that both health-related quality of life and GERD-specific quality of life are improved after surgery compared to medication. Future research will show whether antireflux surgery should be recommended more frequently, for example, to young patients with Barrett´s esophagus.[34] Especially if severity of dysplasia, and therefore future risk of EAC can be assessed (either through gastroscopy and pathology, or biochemistry) a population where a stronger EAC preventive effect could be seen might identified. Performing a RCT large enough to assess and compare the risk of EAC following surgery and medication would mean large methodological, logistic, and ethical difficulties. Therefore, other study designs, such as cohort studies or matched cohorts might be more feasible.

In conclusion, this systematic review and meta-analysis provides some evidence that antireflux surgery may prevent EAC better than medication in patients with Barrett's esophagus, while no such association was found for GERD patients without Barrett's. An increased risk of EAC seems to remain long after antireflux surgery compared to the background population, which might be due to a higher prevalence of Barrett's esophagus. These results must be interpreted cautiously since they are based on a limited sample size and might be affected by bias from severity and duration of GERD, confounding and chance errors. Hence there is a need for larger studies with longer follow-up that take confounding and severity of GERD into account, either by pathologic or molecular assessment of severity.

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Figure 1. Search strategy used in this systematic review and numbers of eligible studies in each stage.

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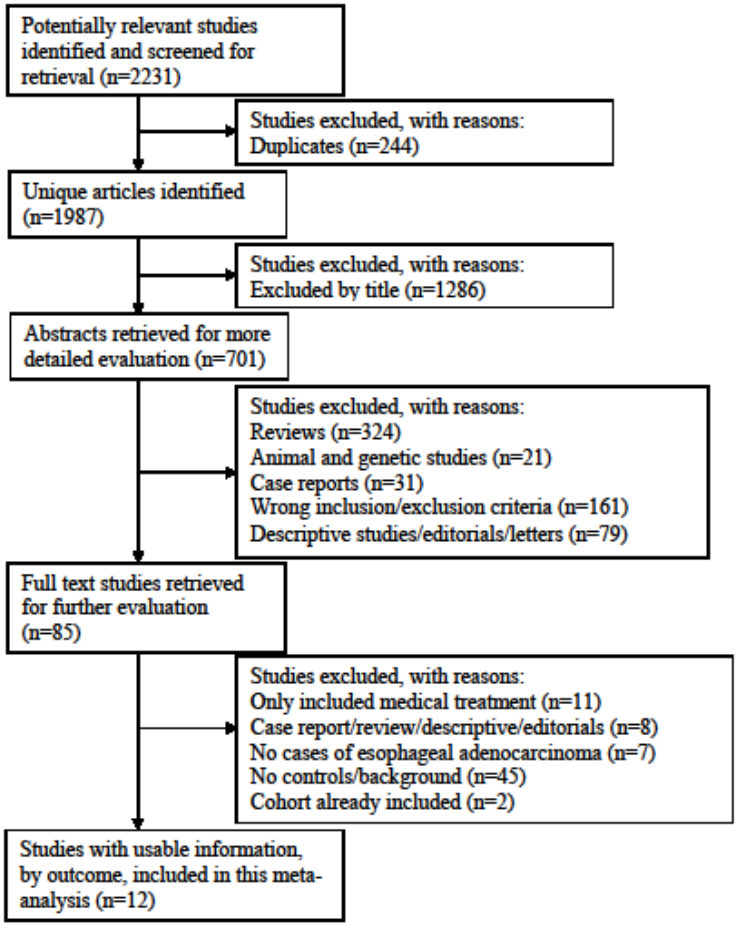
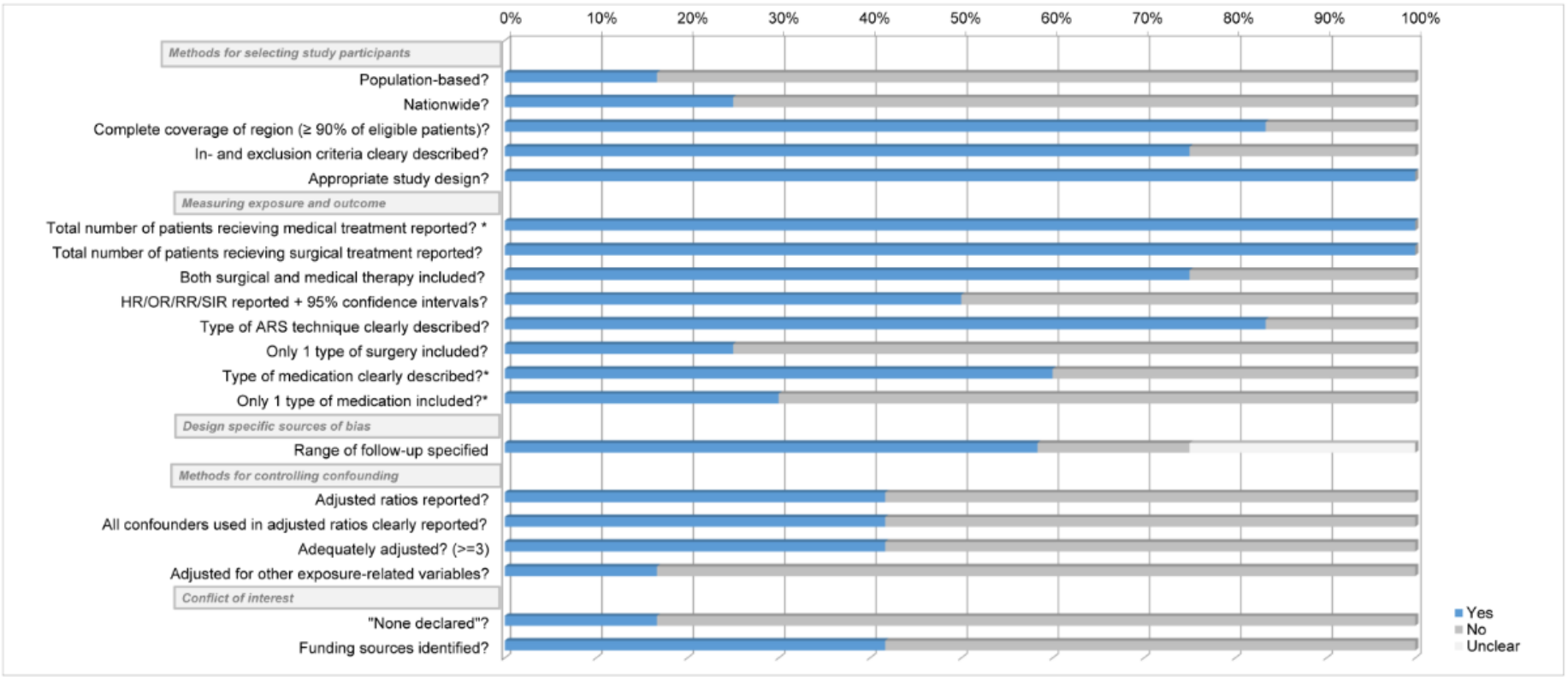


Table 1. Included studies, number of patients, total follow-up times and number of cases of esophageal adenocarcinoma (EAC) in this meta-analysis.

Reference	Year	Country	Type of study	N of patients	Type of surgery	Type of medication	Follow-up (person-years)	Mean (max) follow-up in years	HGD/EAC
Lagergren et al.	2010	Sweden	Population-based	14102 ARS	NF, partial fundoplication	N/A	120514	8.5 (42)	0/39
Kauttu et al.	2011	Finland	Population-based	17643 ARS	NF/partial fundoplication, Roux-en-Y reconstruction	N/A	134438	7.6 (unknown)	0/29
Williamson et al.	1990	USA	Cohort	37 ARS 142 MT	NF ,Collis gastroplasty	N/A	144 198	3.9 (unknown) 1.4 (unknown)	0/3 0/2
McCallum et al.	1991	USA	Cohort	29 ARS 152 MT	NF, Hill gastropexy, Belsey procedure	N/A	150 621	5.2 (unknown) 4.1 (unknown)	0/0 0/2
Attwood et al.	1992	Ireland	Cohort	19 ARS 26 MT	Partial anterior fundoplication	H2RA	57 78	3 (9) 3 (9)	0/1 0/1
Spechler et al.	2001	USA	Randomized controlled study	71 ARS 137 MT	NF	H2RA, PPI, metoclopramide, sucralfate	646 1452	9.1 (unknown) 10.6 (unknown)	0/1 0/4
Ye et al.	2001	Sweden	Cohort	11077 ARS 66965 UR	N/A	Unknown	86996 376622	7.8 (unknown) 5.7 (unknown)	0/43 0/200
Gurski et al.	2003	USA	Cohort	77 ARS 14 MT	NF, partial fundoplication	PPI	323 59	4.2 (unknown) 4.2 (unknown)	3/0 1/0
Parrilla et al.	2003	Spain	Randomized controlled study	58 ARS 43 MT	NF, Collis-Nissen procedure	PPI	406 258	7 (18) 6 (18)	2/0 2/0
Oberg et al.	2005	Sweden	Cohort	46 ARS 94 MT	NF, Hill gastropexy, partial fundoplication	H2RA, PPI	347 599	7.5 (11.5) 6.4 (8.2)	0/0 6/1
Tran et al.	2005	USA	Cohort	946 ARS 1892 MT	Fundoplication	N/A	11156 20115	11.8 (unknown) 10.6 (unknown)	0/8 0/8
Gatenby et al	2009	UK	Cohort	41 ARS 697 MT	N/A	H2RA, PPI	254 3457	6.19 (unknown) 4.96 (unknown)	0/0 10/20

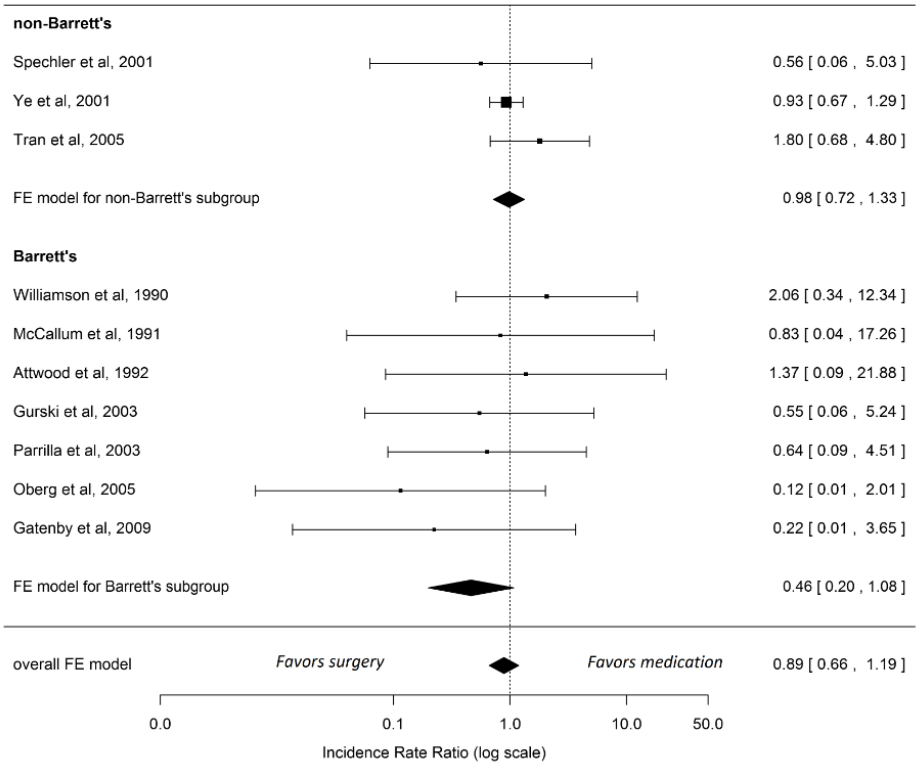
ARS antireflux surgery, N/A not applicable, HGD high grade dysplasia, RCT randomized controlled trial, MT medical treatment, NF Nissen fundoplication (Total fundoplication), H2RA H2-receptor-antagonist, PPI Proton pump inhibitors.

Figure 2. Characteristics and quality assessment of all 12 included studies in this meta-analysis.



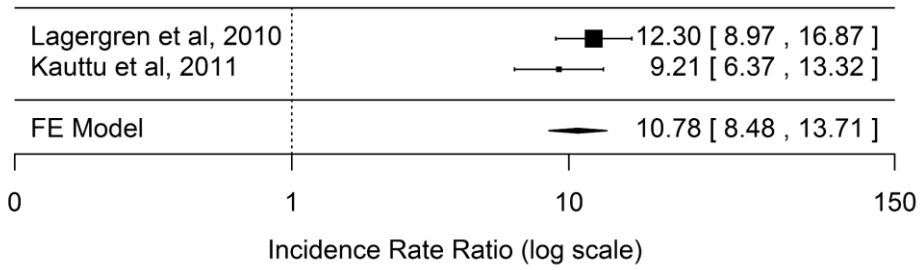
* Excluding 3 studies with non-medicated patients as comparison.

Figure 3. Forrest plot comparing the risk of esophageal adenocarcinoma after antireflux surgery and medical treatment in patients with gastro-esophageal reflux disease with and without Barrett's esophagus.



FE=Fixed-effects

Figure 4. Forrest plot comparing antireflux surgery to an unselected corresponding background population and risk of esophageal adenocarcinoma in this meta-analysis.



FE=Fixed-effects