

**THE INFLUENCE OF ANTI-REFLUX SURGERY ON ESOPHAGEAL CANCER RISK IN ENGLAND –
NATIONAL POPULATION-BASED COHORT STUDY**

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MINI-ABSTRACT

Anti-reflux surgery is used for the treatment of gastro-esophageal reflux disease, a major risk factor for esophageal cancer. This English national population-based cohort study suggested anti-reflux surgery is associated with reduced risk of esophageal cancer in patients with gastro-esophageal reflux disease or Barrett's esophagus.

Word count: 44

STRUCTURED ABSTRACT

Objective: To evaluate how anti-reflux surgery influences the risk of esophageal cancer in patients with gastroesophageal reflux disease (GERD) and Barrett's esophagus.

Background: GERD is a major risk factor for esophageal adenocarcinoma, and the United Kingdom has the highest incidence of esophageal adenocarcinoma globally.

Methods: Hospital Episode Statistics (HES) database was used to identify all patients in England aged over 18 years diagnosed with GERD with or without Barrett's Esophagus from 2000 to 2012, with anti-reflux surgery being the exposure investigated. The Clinical Practice Research Datalink (CPRD) was used to provide a sensitivity analysis comparing proton pump inhibitor therapy and anti-reflux surgery. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated using Cox proportional hazards model with inverse probability weights based on the probability of having surgery to adjust for selection bias and confounding factors.

Results: (i) HES analysis; among 838,755 included patients with GERD and 28,372 with Barrett's esophagus, 22,231 and 737 underwent anti-reflux surgery, respectively. In GERD patients, anti-reflux surgery reduced the risk of esophageal cancer (HR=0.64; 95%CI 0.52–0.78). In Barrett's esophagus patients, the corresponding HR was (HR=0.47; 95%CI 0.12–1.90).

(ii) CPRD analysis; anti-reflux surgery was associated with decreased point estimates of esophageal adenocarcinoma in patients with GERD (0% vs. 0.2%; P=0.16) and Barrett's esophagus (HR=0.75; 95%CI 0.21–2.63), but these were not statistically significant.

Conclusion: Anti-reflux surgery may be associated with a reduced risk of esophageal cancer risk, however it remains primarily an operation for symptomatic relief.

Word count: 243

INTRODUCTION

Esophageal cancer remains in the top five most rapidly rising cancer types in the Western world, [1–3] and the UK has the highest incidence of esophageal adenocarcinoma globally [4]. Many patients present with advanced disease with only 38% of cases able to be treated with a curative intent [5]. Gastroesophageal reflux disease (GERD) is a major risk factor for esophageal adenocarcinoma, with recurrent symptomatic GERD leading to an eight-fold increased risk [6]. The mechanism of the neoplastic process is GERD leading to oesophagitis and metaplastic change in the squamous esophageal epithelium to Barrett’s esophagus and progression with dysplastic changes and then eventually to esophageal adenocarcinoma [7,8].

The mainstay of treatment for GERD is medical with proton pump inhibitors (or H2 antagonists), but anti-reflux surgery is an alternative, usually performed as a laparoscopic partial or total fundoplication [9]. Randomized trials have provided conflicting results when comparing proton pump inhibitor therapy and anti-reflux surgery in the long-term control of GERD symptoms [10,11]. However in recent years, an increasing volume of literature is being published concerning the potential long-term adverse effects of sustained proton pump inhibitor therapy use, including dementia, long-bone fractures and gastric adenocarcinoma [12 – 14].

Previous publications have failed to demonstrate a clear consistent benefit of anti-reflux surgery in reducing the risk of esophageal adenocarcinoma compared to medical therapy [15,16]. However these publications have been limited by small sample sizes, with low numbers of esophageal adenocarcinoma in the long-term follow-up categories, and poorly defined

control populations specifically regarding severity of reflux [16]. The present study seeks to overcome the power limitations as the United Kingdom has the highest Incidence of esophageal adenocarcinoma globally. Furthermore, this study utilized two datasets to evaluate cancer risk following anti-reflux surgery, and also comparing high dose proton pump inhibitor therapy with anti-reflux surgery, and also evaluate a Barrett's esophagus population.

The primary objective of this study was to examine how anti-reflux surgery influences the risk of esophageal cancer in GERD patients. The secondary objectives were to evaluate esophageal cancer risk following anti-reflux surgery in Barrett's esophagus patients and to provide a subset comparison of esophageal cancer risk for patients receiving standard-dose proton pump inhibitor therapy with anti-reflux surgery.

METHODS

Design

This was a national population-based cohort study of anti-reflux surgery conducted in England during the period 2000 to 2012 with follow-up until 2014. Anti-reflux surgery was the main exposure and esophageal cancer was the main outcome. Permissions for the comparison of anonymized administrative data were obtained from the National Information Governance Board for Health and Social Care in England. All procedural and diagnostic codes were independently verified at a local institutional level.

Data sources and definitions

Hospital Episode Statistics Database

Data were derived from the Hospital Episode Statistics (HES) database [17]. This is a record-based system that collects patient-level data from all National Health Service (NHS) hospitals in England. It captures all patients treated in public sector hospitals and all patients treated in privately funded institutions. Patients are given a unique HES identifier that allows all of their hospital admissions to be tracked. The study population consisted of patients aged 18 years or older with a diagnosis of GERD as identified from the International Classification of Diseases version 10 (ICD-10) codes K210 and K219, and patients with Barrett's esophagus using the ICD-10 code K227. Patients receiving anti-reflux surgery were identified using the Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures 4th revision (OPCS-4) codes; primary anti-reflux surgery (G242 – G245, G248 and G249) and revisional anti-reflux surgery (G251, G258, G259). Risk of esophageal cancer (ICD-10 codes C15

and D001) was compared between GERD and Barrett's esophagus patients receiving anti-reflux surgery and those not receiving such surgery. Starting date was taken as the date of GERD diagnosis for both surgical and non-surgical groups.

Because patients undergoing anti-reflux surgery will represent a group of patients with more severe GERD, a sensitivity analysis was performed by linking the HES with the Clinical Practice Research Datalink (CPRD) datasets to mitigate selection bias.

Clinical Practice Research Datalink (CPRD)

Almost 10% of the English population is registered with practices that enter data into the CPRD, formally the General Practice Research Database. About half of all CPRD practices are linked to in-patient HES data, which contain clinical information for each episode of care in English hospitals. Patient linkage was performed centrally using the National Health Service number. Database coverage was from 1997 to 2010, restricted by the end of cancer registry coverage. In CPRD, medcodes are based on the Read clinical coding system for primary care electronic health records developed in England. The study population consisted of patients aged 18 years or older with a diagnosis of GERD or Barrett's esophagus were identified from CPRD data using the relevant Read codes or from the linked HES dataset using the ICD-10 codes described above. Patients undergoing anti-reflux surgery were identified using the relevant OPCS-4 codes described previously and were compared with patients receiving standard dose proton pump inhibitor therapy defined as at least 40mg of esomeprazole, omeprazole or pantoprazole or 30mg of lansoprazole daily for at least one year. The CPRD dataset was linked to the National Cancer Registry, which permitted analysis of only esophageal adenocarcinoma in this subset

analysis. Risk of esophageal adenocarcinoma was compared among participants with GERD and Barrett's esophagus separately receiving anti-reflux surgery and those receiving standard dose proton pump inhibitor therapy. Starting date was taken as the date of GERD diagnosis for both surgical and proton pump inhibitor treatment groups.

Subset analyses

Additional analyses were performed:

(i) Comparison of esophageal cancer risk in patients aged 50 years or older receiving anti-reflux surgery vs. no anti-reflux surgery (HES dataset) or standard dose proton pump inhibitor therapy (CPRD dataset).

(ii) Within the Barrett's cohort, comparison of utilization of EMR or HALO following anti-reflux surgery vs. no anti-reflux surgery (HES dataset) or standard dose proton pump inhibitor therapy (CPRD dataset).

(iii) Within the cohort of patients receiving anti-reflux surgery, analysis of esophageal adenocarcinoma risk in those patients within recurrent reflux (CPRD dataset). This was defined by the requirement standard dose proton pump inhibitor therapy at 6 months after surgery or for revisional anti-reflux surgery within the study period.

Statistical analysis

Categorical variables were expressed as percentages, with intergroup comparisons made using χ^2 test, and continuous variables were expressed as medians and ranges, with intergroup comparisons made using Mann-Whitney U test. Cox proportional hazards models were fitted to

study the long-term esophageal cancer risk in England from both treatment groups. A multivariable model provided hazard ratios (HR) with 95% confidence intervals (CI), adjusted for age (18-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80 years and older), sex (male or female), comorbidity (Charlson comorbidity index 0, 1 or ≥ 2) and obesity (yes or no). Obesity was defined using the ICD-10 code E66 (HES dataset) or a body mass index of $30\text{kg}/\text{m}^2$ within 6 months of diagnosis of GERD (CPRD dataset). Inverse probability weights (IPW) were applied to correct for confounding and selection bias. Firstly, a logistic model was fitted to calculate the probability of having an anti-reflux surgery and the predicted values were used to calculate the inverse probability weights that were afterwards applied in the logistic models for esophageal cancer models. Survival curves were also obtained using the inverse probability weights [18]. Statistical analysis was performed using SPSS version 22.0 software (Statistical Package for the Social Sciences software, Version 22, SPSS Chicago (IL), USA) and using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Hospital Episode Statistics analysis

GERD patients aged 18 years or older receiving anti-reflux surgery vs. no such surgery

Over the study period, 838,755 patients aged 18 years or older were diagnosed with GERD and included, of these 22,231 (2.7%) underwent anti-reflux surgery. Patients undergoing anti-reflux surgery were younger (median age 47 vs. 59 years; $P<0.01$), more commonly male (56% vs. 52.3%; $P<0.01$) and obese (6.1% vs. 4.2%; $P<0.01$), and less commonly having Charlson score of ≥ 2 (1.6% vs. 3.3%; $P<0.01$) (Table 1). The median follow-up period was 5.4 and 6.4 years in anti-reflux surgery and non-surgery groups. Anti-reflux surgery was associated with a reduced risk of esophageal cancer (adjusted HR 0.64; 95% CI 0.52–0.78) (Table 2) (Figure 1).

Barrett's esophagus patients aged 18 years or older receiving anti-reflux surgery vs. no such surgery

Over the study period, 28,372 patients aged 18 years or older were diagnosed with Barrett's esophagus and were included, and 737 (2.6%) underwent anti-reflux surgery. Similar to the GERD cohort, patients with Barrett's esophagus undergoing anti-reflux surgery were younger, more commonly obese and less commonly had Charlson score of ≥ 2 (Table 1). The median follow-up period was 5.6 and 4.9 years in anti-reflux surgery and non-surgery groups, respectively. Anti-reflux surgery was associated with decreased point estimates of esophageal cancer (adjusted HR 0.47; 95% CI 0.12–1.90) (Table 2) (Figure 2).

Within the Barrett's cohort the proportion of patients requiring EMR or HALO was similar following anti-reflux surgery (0.90%, 7 from 775 patients) compared with no anti-reflux surgery (1.59%, 439 from 27683 patients) ($P=0.442$).

Subset analysis: GERD patients aged 50 years or older receiving anti-reflux surgery vs. no such surgery

Over the study period, 580,293 patients aged 50 years or older were diagnosed with GERD in HES. Of these, 9,753 patients (1.7%) underwent anti-reflux surgery. The median follow-up period was 5.4 and 6.4 years in anti-reflux surgery and non-surgery groups, respectively. Anti-reflux surgery was associated with a reduced risk of esophageal cancer (adjusted HR 0.75; 95% CI 0.58–0.97) (Table 2).

Subset analysis: Barrett's esophagus patients aged 50 years or older receiving anti-reflux surgery vs. no such surgery

Over the study period, 22,901 patients aged 50 years or older were diagnosed with Barrett's esophagus. Of these 432 patients (1.9%) received anti-reflux surgery. The median follow-up period was 5.6 and 4.9 years in anti-reflux surgery and non-surgery groups, respectively. Anti-reflux surgery was associated with decreased point estimates of esophageal cancer (adjusted HR 0.76; 95% CI 0.19–3.09), but statistically non-significant (Table 2) (Figure 2).

Clinical Practice Research Datalink analysis

GERD patients aged 18 years or older receiving anti-reflux surgery vs. high-dose proton pump inhibitor therapy

16,938 patients aged over 18 years with GERD and on high dose proton pump inhibitor therapy were included in this analysis. From this cohort 1116 patients (6.6%) underwent anti-reflux surgery with the remaining 15,822 patients had proton pump inhibitor therapy alone. The median follow-up period was 5.2 and 5.3 years in anti-reflux surgery and high dose proton pump inhibitor therapy groups, respectively. Patients undergoing anti-reflux surgery were younger (median age 48 vs. 60 years; $P<0.01$), more commonly male (50.2% vs. 43.3%; $P<0.01$) and less commonly having Charlson score of ≥ 2 (9.1% vs. 20.9%; $P<0.01$), however there was no significant difference in the incidence of obesity between groups (2.1% vs. 2.5%; $P=0.39$). The prevalence of esophageal adenocarcinoma was decreased following anti-reflux surgery, but was not statistically significant (0% vs. 0.2%; $P=0.16$). No esophageal adenocarcinoma events were identified in the anti-reflux surgery cohort, which prevented the calculation of hazard ratios for this result.

Barrett's esophagus patients aged 18 years or older receiving anti-reflux surgery vs. high-dose proton pump inhibitor therapy

Over the study period, 786 patients aged over 18 years with Barrett's esophagus were included in this analysis. From this cohort 166 patients (21.1%) underwent anti-reflux surgery and 620 patients (78.9%) were treated with high dose proton pump inhibitor treatment, of these 3 (1.8%) and 18 (2.9%) patients were diagnosed with esophageal cancer during the study period, respectively. The median follow-up period was 5.8 years in both groups. Patients undergoing anti-reflux surgery were younger (median age 52 vs. 64 years; $P<0.01$), less commonly male (59.0% vs. 66.0%; $P=0.10$) and with Charlson score of ≥ 2 (9.0% vs. 19.4%; $P<0.01$), however

there was no significant difference between the groups in the incidence of obesity (1.8% vs. 1.1%; $P=0.49$). Anti-reflux surgery was followed by a decreased point estimate of esophageal adenocarcinoma, but this was not statistically significant (adjusted HR=0.75; 95% CI 0.21–2.63) (Figure 3).

16 patients (2.0%) underwent HALO or EMR after the first recording of reflux or anti-reflux surgery. Of these two (1.2%) underwent anti-reflux surgery and the remaining 14 patients (2.3%) received standard dose proton pump inhibitor only ($P=0.32$).

Subset analysis: GERD patients aged 50 years or older receiving anti-reflux surgery vs. high-dose proton pump inhibitor therapy

11,727 patients aged over 50 years with GERD and on high dose proton pump inhibitor therapy were included in this analysis. From this cohort 518 patients (4.4%) underwent anti-reflux surgery with the remaining 11,209 patients had proton pump inhibitor therapy alone. The median follow-up period was 5.2 and 5.3 years in anti-reflux surgery and high dose proton pump inhibitor therapy groups, respectively. The prevalence of esophageal adenocarcinoma was decreased following anti-reflux surgery, but was not statistically significant (0% vs. 0.2%; $P=0.26$). No cancer events were identified in the anti-reflux surgery cohort, which prevented the calculation of hazard ratios for this result.

Subset analysis: Barrett's esophagus patients aged 50 years or older receiving anti-reflux surgery vs. high-dose proton pump inhibitor therapy

Over the study period, 622 patients aged over 50 years with Barrett's esophagus were included in this analysis. From this cohort 92 patients (14.8%) underwent anti-reflux surgery and 530 patients (85.2%) were treated with standard dose proton pump inhibitor treatment, of these 3 (3.3%) and 18 (3.4%) patients were diagnosed with esophageal adenocarcinoma during the study period, respectively. The median follow-up period was 5.5 and 5.7 years in anti-reflux surgery and high dose proton pump inhibitor treatment groups, respectively. Anti-reflux surgery was followed by a decreased point estimate of esophageal adenocarcinoma, but this was not statistically significant (adjusted HR=0.77; 95% CI 0.21–2.78).

Subset analysis; Patients with recurrent reflux following anti-reflux surgery

From 2000 to 2010, 1116 patients underwent anti-reflux surgery, of which 335 (30.0%) were on proton pump inhibitor therapy six months after surgery and 51 (4.6%) underwent revisional anti-reflux surgery. No cancer events were noted in either group.

DISCUSSION

This large population-based cohort study suggests that patients with GERD who undergo anti-reflux surgery are at a reduced risk of esophageal cancer when compared to non-operated patients with GERD. Although limited by low statistical power, also when compared to GERD patients on proton pump inhibitor therapy, anti-reflux surgery suggested a decreased risk of esophageal cancer, and similar indications were found for patients with Barrett's esophagus.

The results of this study contradict some previous national population-based cohort studies, which showed that anti-reflux surgery does not consistently reduce the risk of esophageal adenocarcinoma compared to medical therapy in patients with GERD [19–21]. This might be a reflection of the large sample size studied and the relatively high incidence of esophageal cancer within the population studied, compared to previous publications. When considering the clinical implications of this study, the long-term adverse effects of proton pump inhibitor use must also be considered in patients with chronic GERD [12–14]. These adverse outcomes must be balanced against the short-term and long-term complications of anti-reflux surgery, although recent data does suggest that anti-reflux surgery is a very safe procedure with a 30-day mortality rate of 0.03% [22]. The main analysis from the present study to demonstrate a statistically significant reduction in esophageal cancer risk was seen in the very large cohort including over 800,000 patients with over 20,000 patients receiving ARS. This does suggest the absolute reduction in esophageal cancer risk from anti-reflux surgery is small and requires a large number of patients to be studied in order to demonstrate any statistically significant reduction. In this study, patients with Barrett's esophagus were also studied as a population at

increased risk of developing esophageal adenocarcinoma [23]. Although hampered by low precision, when GERD severity was accounted for by comparison of proton pump inhibitor therapy with anti-reflux surgery, there were similar reductions in the risk esophageal cancer associated with anti-reflux surgery, which again contradicts results from previous studies [24–26].

The mechanism of the reduced cancer risk seen with anti-reflux surgery when compared with non-surgical or medical treatment of GERD is multi-factorial. Anatomically anti-reflux surgery creates a barrier against the reflux of gastric contents into the lower end of the esophagus reducing the pro-inflammatory and carcinogenic process [27]. Medical treatment mainly does not mechanically prevent reflux, but does decrease the acidity of the refluxed content. Importantly, previous randomized controlled trials have showed a lower level of esophageal pathological acidity at 5-year followup after anti-reflux surgery compared with medication [28]. Also anti-reflux surgery is an intervention that is not dependent upon dose or compliance, which is a limitation of medical therapy for GERD.

The population-based design with virtually complete inclusion of all eligible patients in England is strength of the study. The large sample size, complete follow-up of all patients, and the adjustment for several relevant confounding factors are other advantages. There are also limitations. The reliability of the methodology and accuracy of data collection is a limitation of most national administrative databases. From the national dataset utilized it was not possible to identify the diagnostic workup for GERD, including use of pH studies, which may have shown

heterogeneity across the country. Patients receiving anti-reflux surgery often have failed medical therapy and thus often have a more severe form of GERD, suggesting a potential selection bias of the HES analysis. However, this selection bias was reduced in the CPRD analysis comparing patients on proton pump inhibitor therapy with anti-reflux surgery. An additional subset analysis was also performed on patients aged 50 years and older to reduce any selection bias demonstrating similar findings, because younger patients maybe more likely to receive anti-reflux surgery [29]. Furthermore, although all analyses were adjusted for patient age, sex, obesity and comorbidity, there may have been unmeasured factors, that may have confounded the results. The incidence of esophageal cancer was low within the study cohort, but yet greater than previous publications in this field [16], because of the relatively high incidence of esophageal adenocarcinoma in England [4]. Yet, the statistical power was inadequate for the secondary analyses, documented by the wide confidence intervals. However, all analyses consistently indicated reduced risk of esophageal cancer in the anti-reflux surgery groups, indicating validity.

In conclusion, the results of this national English population-based cohort study of patients with GERD, indicates that anti-reflux surgery is associated with a reduction in the risk of esophageal cancer. This reduction was suggested also in patients with Barrett's esophagus undergoing anti-reflux surgery. However, the absolute reduction is small and therefore patients should be counseled that anti-reflux surgery is primarily an operation for symptomatic relief from GERD.

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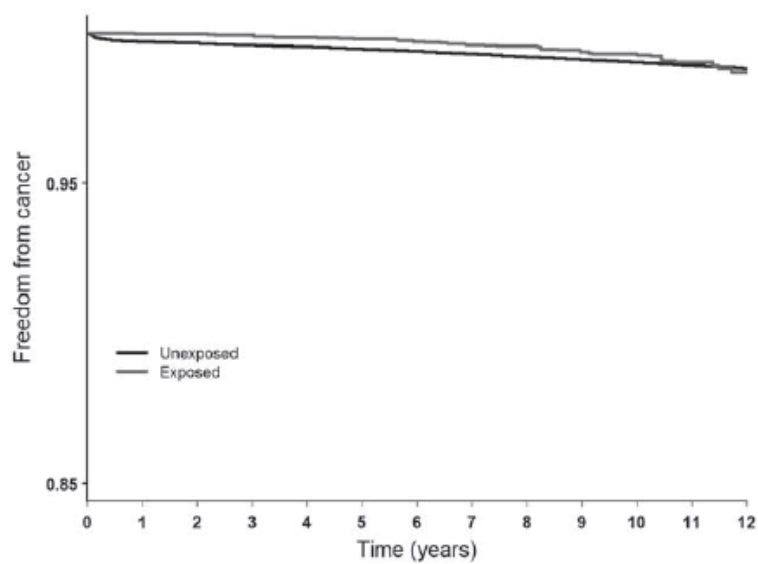
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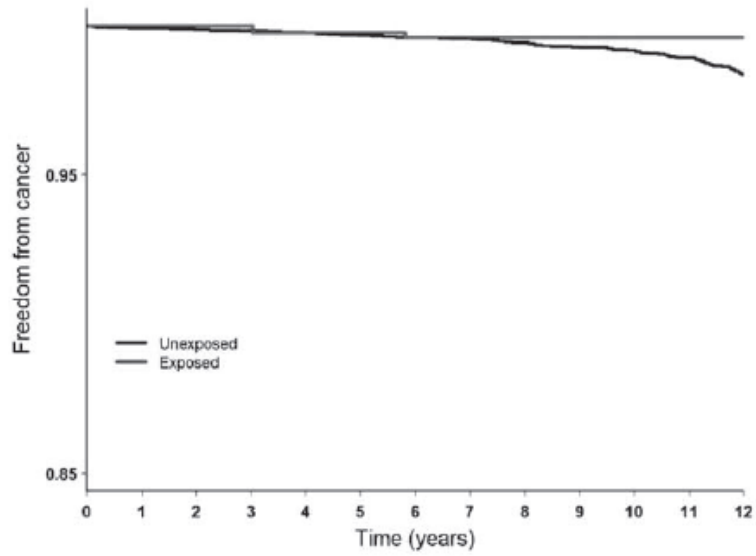
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FIGURES



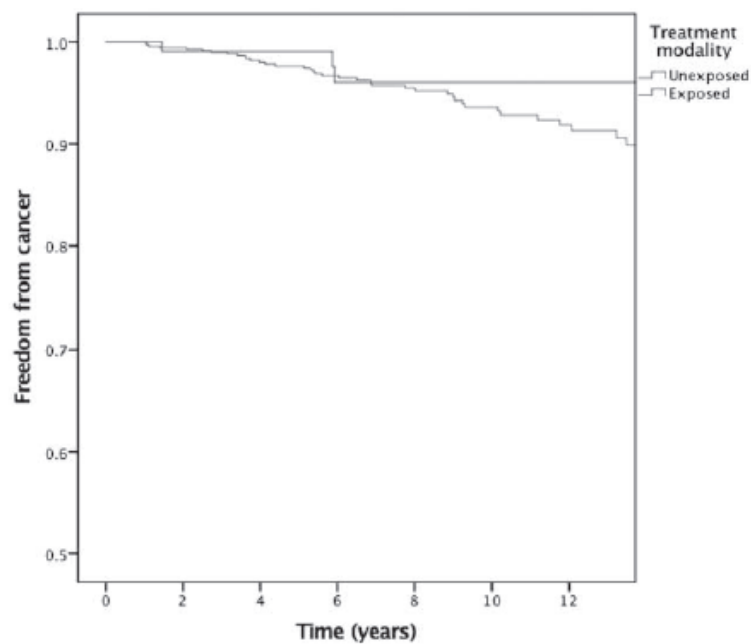
Time	0	1	2	3	4	5	6	7	8	9	10	11	12
Unexposed	816524	748178	675368	607976	544455	481854	422602	364971	310924	255676	195291	132850	69515
Exposed	22231	18469	16468	14713	13018	11421	9910	8553	7255	5902	4511	3017	1630

Figure 1: Kaplan Meier plot showing a reduction in freedom from esophageal cancer in GERD patients receiving no surgery (unexposed) compared with those receiving anti-reflux surgery (exposed) from HES database (HR=0.64; 95%CI 0.52–0.78; P-value:<0.01).



Time	0	1	2	3	4	5	6	7	8	9	10	11	12
Unexposed	27635	26624	23946	19380	16854	13911	11723	9755	8153	6747	5315	3843	2215
Exposed	737	681.5	620.1	503.7	434.3	362.5	298.8	249.4	213.3	172	135.4	97.1	54.5

Figure 2: Kaplan Meier plot showing no significant difference in freedom from esophageal cancer in Barrett’s esophagus patients receiving anti-reflux surgery (exposed) vs. no surgery (unexposed) from HES database (HR=0.47; 95%CI 0.12–1.9; P-value: 0.29).



Time	0	1	2	3	4	5	6	7	8	9	10	11	12
Unexposed	620	726	686	632	570	521	453	396	346	296	245	211	173
Exposed	166	116	103	91	83	75	62	56	47	36	30	25	17

Figure 3: Kaplan Meier plot showing no significant difference in freedom from esophageal cancer in Barrett's esophagus patients receiving anti-reflux surgery (exposed) vs. proton pump inhibitor treatment (unexposed) from CPRD database (HR=0.75; 95%CI 0.21–2.63).

TABLES

Variables	HES Database			CPRD Database		
	ARS (n = 22,231)	No ARS (n = 816,524)	P Value	ARS (n = 1116)	PPI Therapy (n = 15,822)	P Value
GERD patients						
Age (median (IQR))	47 (38–57)	59 (47–70)	<0.01	48 (37–59)	60 (47–70)	<0.01
Male sex (%)	12,449 (56)	427,042 (52.3)	<0.01	560 (50.2)	6851 (43.3)	<0.01
Charlson score (%) ≥ 2	356 (1.6)	26,700 (3.3)	<0.01	102 (9.1)	3307 (20.9)	<0.01
Obesity	1356 (6.1)	34,294 (4.2)	<0.01	23 (2.1)	396 (2.5)	0.39
Esophageal cancer (%)	67 (0.3)	5716 (0.7)	<0.01	0 (0)	32 (0.2)	0.16
Barrett Esophagus Patients						
	ARS (n = 737)	No ARS (n = 27,635)	P Value	ARS (n = 166)	PPI Therapy (n = 620)	P Value
Age (Median (IQR))	52 (44–60)	61 (52–69)	<0.01	52 ()	64 ()	<0.01
Male sex (%)	500 (67.9)	18,902 (68.4)	0.751	98 (59)	409 (66)	0.10
Charlson score (%) ≥ 2	8 (1.1)	691 (2.5)	<0.01	15 (9)	120 (19.4)	0.01
Obesity	51 (6.9)	1409 (5.1)	0.04	3 (1.8)	7 (1.1)	0.49
Esophageal cancer (%)	2 (0.3)	166 (0.6)	0.45	3 (1.8)	18 (2.9)	0.44

TABLE 1. Comparison of Demographics Between Patients Aged 18 Years or Older Receiving Antireflux Surgery or Conservatively Managed With GERD or Barrett Esophagus

Analyses	Patients Aged 18 Years or Older (HES Dataset)		Patients Aged 50 Years or Older (HES Dataset)		Patients Aged 18 Years or Older (CPRD Dataset)		Patients Aged 50 Years or Older (CPRD Dataset)	
	Esophageal Cancer		Esophageal Cancer		Esophageal Adenocarcinoma		Esophageal Adenocarcinoma	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
Univariate Cox model antireflux surgery in GERD patients	0.39 (0.30–0.50)	<0.01	0.54 (0.40–0.72)	<0.01	*	*	*	*
Adjusted antireflux surgery in GERD patients	0.64 (0.52–0.78)	<0.01	0.75 (0.58–0.97)	0.03	*	*	*	*
Univariate Cox model antireflux surgery in Barrett patients	0.45 (0.10–1.99)	0.30	0.45 (0.07–3.03)	0.41	0.62 (0.18–2.11)	0.44	0.99 (0.29–3.33)	0.99
Adjusted antireflux surgery in Barrett patients	0.47 (0.12–1.90)	0.29	0.76 (0.19–3.09)	0.71	0.75 (0.21–2.63)	0.69	0.77 (0.21–2.78)	0.60

*Unable to calculate as no cancer events in the antireflux surgery group.

TABLE 2. Unadjusted and Adjusted Risk of Esophageal Cancer Following Antireflux Surgery in Patients With GERD or Barrett Esophagus