Esophageal adenocarcinoma arising after antireflux surgery: a population-based analysis

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Abstract

Objective: Fundoplication is widely used to treat gastroesophageal reflux disease (GERD). Whether it diminishes the development of esophageal adenocarcinoma (EAC) is, however, controversial. Our aim was to define, at the national level in Finland, frequency and predisposing factors for post-fundoplication EAC. Methods: For this population-based study from 1980 to 2006, Finland’s administrative databases provided preliminary data. Analyses of EAC patient records (N = 1035) led us to include those with preceding antireflux surgery. Conservatively treated patients were not analyzed. The EAC incidence in patients with antireflux surgery was compared with that in the general population (1987–2006) by means of standardized incidence ratio (SIR). Results: A total of 53 (5.1%) EAC patients had undergone antireflux surgery. Of these patients with male predominance (74%), preoperatively 41 (77%) had developed endoscopic esophagitis, 40 (75%) hiatal hernia, 24 (45%) Barrett’s esophagus (BE), nine (17%) ulcer in the esophagus or gastroesophageal junction, and three (6%) stricture. Postoperatively, histologically confirmed BE was present in 42 (79%). Antireflux surgery had preceded EAC at a mean interval of 10.1 years (range 0.5–25.6 years). This interval was significantly (p = 0.02) shorter in patients with long-term functioning fundoplication (n = 15; 30%) at EAC diagnosis (6.4 years, range 0.5–15.2 years) than in those (n = 22, 44%) with failure (11.2 years, range 4.0–24.3 years). Overall, the SIR for EAC after antireflux surgery (1987–2006) was 9.21. Conclusions: Intention-to-treat GERD with antireflux surgery does not prevent EAC. It often develops more than 5 years postoperatively, also in the patients with a good antireflux barrier. Only one-third of the patients had, however, a functioning fundoplication. Preoperative BE and endoscopic esophagitis may be risk factors. Prospective, long-term, randomized studies in experienced centers may reveal the definite effect of antireflux surgery on EAC development.

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Keywords: Fundoplication; Esophageal adenocarcinoma; Gastroesophageal reflux disease

1. Introduction

The incidence of esophageal adenocarcinoma (EAC) is rapidly rising. The major risk factors for EAC are gastroesophageal reflux disease (GERD) and Barrett’s esophagus (BE) [1,2]. In both GERD and BE, gastroesophageal reflux causes esophageal mucosal damage with chronic inflammation. Inflammation, in general, is an important risk factor for cancer development [3]. Antireflux surgery is usually performed to treat patients with serious GERD, and these operations lead to good control of reflux; but their effect on development of EAC is, however, disputable.

Most studies on the effectiveness of antireflux surgery in preventing EAC have focused on BE patients, their results being contradictory. In a randomized trial and in a meta-analysis, surgery and medical treatment proved equally ineffective [4,5]. Conversely, several studies with follow-up ranging from 1.5 to 6.2 years have favored surgical antireflux treatment in preventing progression and inducing regression of dysplastic Barrett’s epithelium [6–10]. EAC appearing after antireflux surgery has been frequently detected either shortly after antireflux surgery [11,12] or in patients with recurrence of GERD [5,13], either with or without preoperative low-grade dysplasia [5,12].

In studies on GERD patients with or without BE, antireflux surgery and medical treatment of GERD were equally ineffective in preventing EAC in a randomized controlled trial [14]. In a cohort study, risk for EAC after antireflux surgery was lower than in controls, but there was a trend in favor of surgery [15]. The risk of developing EAC is four times higher in GERD patients [16]. The risk of EAC development is significantly increased if a patient has GERD, BE, and esophagitis [17]. Antireflux surgery decreases the risk of developing EAC [18]. The aim of this study was to define the incidence of EAC in patients with antireflux surgery.
surgery was higher than in patients with non-surgical GERD treatment [2]. Another cohort study found no significant difference between surgical and medical treatment [15]. At population level, EAC risk after antireflux surgery has recently been reported to be increased 12-fold [16].

Studies of the molecular changes occurring in the GERD—EAC sequel have revealed conflicting evidence, as well. For instance, oxidative stress of the esophageal mucosa remained increased even 4 years after successful fundoplication and the healing of macroscopic esophagitis [17].

Because of these conflicting findings, we conducted a long-term population-based study of EAC after antireflux surgery in Finland, whose national registries have proven to be of high validity [18,19]. The aim was to determine the incidence of EAC occurring after antireflux surgery, and factors contributing to it.

2. Methods

Baseline data for this study were provided by three of Finland’s administrative databases: the Finnish Cancer Registry, Statistics Finland, and the National Institute for Health and Welfare. The study protocol was approved by the Ethics Committee of the Department of Surgery, Helsinki University Central Hospital, and by the Finnish Ministry of Social Affairs and Health.

2.1. Data collection on EAC and antireflux surgery

All cancers in Finland must be reported to the Finnish Cancer Registry. For solid tumors, its coverage exceeds 99% [18]. According to this registry, between January 1980 and December 2006, a total of 1035 EAC cases were diagnosed in Finland (population ~5.3 million). Its mean annual incidence rate was 38 per year, with a range of 7–93, rising during the study period. Hospital and case records of these EAC patients were obtained from public and private health-care units. Their detailed analysis revealed patients with previous antireflux surgery. Death certificates were ordered from Statistics Finland for those EAC patients with incomplete information.

Detailed information on those patients with any type of antireflux surgery (n = 53) prior to diagnosis of EAC provided the following factors: sex, history of GERD, presence of BE, use of antireflux medication, examination results for GERD, smoking, alcohol use, time and type of antireflux surgery, long-term outcome of surgery, and diagnosis and location of EAC. Data on tumor location were missing in only one case. All other cancers (n = 52, 98%) were located in the esophagus or at the gastroesophageal junction. According to the 6th edition of classification of esophageal and esophagogastric junctional tumors by the American Joint Committee on Cancer, the tumors could be classified either as esophageal in origin (C15.1, C15.4, C15.5, or C15.9) or cardiac/esophagogastric junctional (C16.0).

Since 1987, all Finnish hospitals licensed to perform surgery have been required to report every patient to the National Institute for Health and Welfare (THL). Therefore, the data on antireflux surgeries were only available since 1987. Between January 1987 and December 2006, 19 542 operations were performed for GERD with a mean annual 977 antireflux operations (range 408–1543). During this period, 1999 (10.2%) patients with antireflux surgery also had a cholecystectomy. For the analysis of the effect of antireflux surgery on EAC incidence, 17 643 patients were eligible. Patients were excluded due to incorrect or duplicate identification numbers, and uncertainty of dates.

2.2. Statistical analysis

The influence of antireflux surgery on EAC incidence was assessed by comparing the observed EAC incidence in antireflux surgery patients to an expected rate based on the age- (10-year groups), sex-, and calendar-period-matched Finnish population in 1987–2006. This standardized incidence ratio (SIR) was calculated in the Finnish Cancer Registry. Follow-up for EAC started from the year following antireflux surgery, and ended at death, emigration (data from the Finnish Population Register Centre), or EAC diagnosis.

Except for the incidence calculation, statistical analysis of the data was performed with Statistical Package for Social Sciences (SPSS) software, versions 14.0–16.0 (SPSS Inc., Chicago, IL, USA). The mean, median, minimum, and maximum served as descriptive statistics. Statistical differences were calculated by unpaired t-test for continuous variables, and by chi-square or Fisher’s exact test for categorical variables. A p value <0.05 was considered statistically significant.

2.3. Role of the funding source

The study was funded by Helsinki University Central Hospital Research Funds (EVO) and by the Pirkanmaa Cultural Foundation. The funding sources did not participate in the design, conduct, or reporting of the study.

3. Results

The EAC incidence in patients treated with antireflux surgery was 9.2-fold that of the general Finnish population (Table 1). The increase in risk was similar in both men and women. In total, antireflux surgery had preceded the diagnosis of EAC in 53 patients, with mean age at antireflux surgery of 54.6 years (range 27–80 years), and, at EAC diagnosis, 64.7 years (range 29–89 years). Of these, 39 (74%) were male, 19 (36%) were smokers, and 11 (21%) consumed substantial amounts of alcohol.

After the antireflux surgery, EAC was diagnosed after a median period of 8.8 years, and with a mean interval of 10.1 years (range 0.5–25.6 years). Three-quarters of these cancers appeared more than 5 years, and 43% more than 10 years postoperatively. EAC was diagnosed at endoscopic surveillance in 21 (40%), at endoscopy performed due to symptoms in 24 (45%) (dysphagia 22, weight loss 13, anemia 3), in a search for the primary tumor in one (2%), and for some other reason in seven (13%).
Table 1. Risk for esophageal adenocarcinoma (EAC) after antireflux surgery in comparison with that of the general population.

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
<th>Males + females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>10,027</td>
<td>7,616</td>
<td>17,643</td>
</tr>
<tr>
<td>Person-years</td>
<td>76,734.5</td>
<td>57,703.7</td>
<td>134,438.2</td>
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<tr>
<td>Observed EAC (n)</td>
<td>25</td>
<td>4</td>
<td>29</td>
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<tr>
<td>Expected EAC (n)</td>
<td>2.7</td>
<td>0.5</td>
<td>3.2</td>
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<tr>
<td>SIR</td>
<td>9.32</td>
<td>8.57</td>
<td>9.21</td>
</tr>
<tr>
<td>95% CI</td>
<td>6.03—13.75</td>
<td>2.34—21.95</td>
<td>6.17—13.22</td>
</tr>
</tbody>
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SIR: standardized incidence ratio, CI: confidence interval.
* p ≤ 0.001.
** p < 0.01.

3.1. GERD before antireflux surgery

Of the 53 patients, data on GERD symptoms preceding antireflux surgery were available for 38 (72%), 34 (69%) of whom had at least one of the classical symptoms of GERD (heartburn and regurgitation). Other symptoms included for example, upper abdominal pain and dysphagia. Conservative treatment of the patients with available data was common: 38 (97%) of 39 had used some form of medication for GERD, 31 (79%) of whom had used either proton pump inhibitors or histamine H₂-receptor antagonists. Data on preoperative studies for GERD were missing for four patients (7%). A majority of the patients underwent antireflux surgery for ascertained erosive esophagitis or BE (Table 2). An additional three patients had a diagnosis of hiatal hernia.

BE was diagnosed before antireflux surgery in 24 patients (45%), and additionally postoperatively in nine (17%), and, at the time of EAC diagnosis, in nine others (17%). Therefore, a total of 42 patients (79%) had BE with a histological confirmation, including two already with dysplasia before fundoplication. Patients with preoperative BE had a mean antireflux surgery-to-EAC interval of 8.4 years (range 0.5—25.8 years) compared with 11.6 years (range 2.0—25.2 years) in other patients; p = 0.068.

3.2. Antireflux surgery

The type of final antireflux surgery was fundoplication in 50 (of which eight (15%) were laparoscopic) and partial gastrectomy with Roux-en-Y reconstruction in four. The type of fundoplication, whether total or partial, could be assessed for 44 patients: 42 (95%) complete and two (5%) partial fundoplications; nine patients had a concomitant vagotomy. Of the Roux-en-Y duodenal diversions, one was originally combined with a fundoplication, one was performed without fundoplication, and two after failed fundoplications. The interval to diagnosis of EAC in these patients was, on average, 13.5 years (range 8—25 years). Re-operations had been necessary for four patients, in whom EAC appeared, on average, 17 years (range 8—25 years) after the last re-operation.

Together with antireflux surgery, cholecystectomy was performed on 12 patients, and after antireflux surgery on three patients. In these 15 patients (28%), cholecystectomy preceded the diagnosis of EAC at an average interval of 17.5 years (range 7—33 years). Cholecystectomy was performed on 14 (33%) patients with BE.

3.3. Functional state of the fundoplication

Of the patients with fundoplication (n = 50), fundoplication was ascertained to be anatomically normal in 23 patients (46%) at the time of endoscopic detection of or surgery for EAC. Anatomic failure was detected in 13 (26%) patients, at a mean interval of 11.5 years (range 2—23 years) after the primary fundoplication. In 14 (28%) others, no information was available as to the postoperative anatomy of the fundoplication. Those patients with an anatomically normal fundoplication developed EAC earlier (p = 0.0069) after the primary fundoplication (mean 7.0 years, range 0.5—17.5 years) than did those with an anatomically failed fundoplication (mean 12.0 years, range 4.0—22.9 years).

Recurrence of hiatal hernia or widening of the hiatal crura was evident in 22 (44%) patients, with three (6%) fundoplications situated in the thoracic cavity. Overall, failure of surgery – that of the fundoplication itself or of the hiatal closure – was detectable in 27 (54%) patients.

To assess the real effectiveness of the fundoplication, both the anatomy of the fundoplication and indicators of reflux were considered. Functional failure of the antireflux barrier was detectable in 22 (44%) patients (Fig. 1), when the anatomic failure of the fundoplication was combined with objective indicators of postoperative reflux: recurrent endoscopically evident esophagitis (n = 11), pathologic pH monitoring (n = 4), pathologically low pressure of the lower esophageal sphincter.

![Fig. 1. Functional state of the fundoplication, and time-interval between fundoplication and esophageal adenocarcinoma (EAC).](https://academic.oup.com/ejcts/article-abstract/40/6/1450/421467)
esophageal sphincter (LES, n = 1), and recurrent symptoms of regurgitation (n = 3). Fifteen patients (30%) had a good long-term outcome, and for 13 (26%) patients, information for evaluation was insufficient. Those with a good long-term outcome developed EAC earlier (p = 0.015) after the primary fundoplication (mean 6.4 years, range 0.5–15.2) than did those with a failure (mean 11.2 years, range 4.0–24.3 years) (Fig. 1). The patients facing EAC shortly after fundoplication had either normal function of the fundoplication, or the function was unknown. Particularly, of the three EACs diagnosed <2 years (6, 14, and 18 months) after the fundoplication, all with a preoperative diagnosis of BE, one had non-specific dysplasia seen once among several endoscopies already before fundoplication, and one had low-grade dysplasia shortly after the fundoplication. Of the patients with long-term functioning fundoplication, 73% had a preoperative diagnosis of BE, as compared with 41% in those with a failed fundoplication (p = 0.052). Of the two patients with pre-fundoplication dysplasia, one had a functioning fundoplication at the time of EAC, and the other had Roux-en-Y duodenal diversion after two failed fundoplications.

Overall, at some point after antireflux surgery, 21 (40%) of the patients received medical treatment either by proton pump inhibitors (15; 28%) or by H₂-receptor antagonists (9; 17%). No difference appeared in the use of medical treatment between patients with functioning or failed fundoplication (p = 0.44), or between patients with anatomically normal or failed fundoplication (p = 0.88).

4. Discussion

According to this national population-based study, EAC develops after antireflux surgery in a significant number of patients. Of our EAC patients, 53 (5.1%) developed EAC after antireflux surgery during a timeline of 26 years. The EAC incidence remained increased after antireflux surgery — it was approximately 9 times as high as in the general population.

Laparoscopic antireflux surgery has evidently lowered the threshold for surgery, and has even been marketed as a curative treatment option. In addition, antireflux operations may also play a role in the prevention of EAC, the development of which is associated with GERD.

The major limitation of our study was the lack of a comparison group of medically treated GERD patients. Due to the high prevalence of severe GERD (BE and endoscopic esophagitis) in our patients, the cancer risk was also higher at baseline. It may be that, already at this phase, the cellular transformation is not reversible. Whether the progression to EAC can be halted by any treatment method must be determined in studies comparing the surgical and medical treatments. Previously, however, the EAC risk has been reported to be even higher after surgical than non-surgical treatment of GERD at a population level [2]. Our data are also well in line with Lagergren’s finding of a 12-fold increased EAC risk after antireflux surgery, where the risk also remained high at long follow-up [16].

The assessment of healing of GERD after antireflux surgery without objective evidence — that is, endoscopy, pH measurement, or manometry — is very difficult. Symptoms (except for regurgitation) and postoperative usage of acid-suppression medication are not sufficiently reliable indicators of postoperative reflux. We detected a considerable rate of objectively measured failure of the fundoplication, that of the fundoplication itself (26%), or of incomplete inhibition of reflux (44%). This relatively high failure rate suggests that this surgery should only be performed in well-experienced centers with a sufficient yearly volume of procedures. Importantly, however, the anatomic failure of fundoplication was detected as late as, on average, 11.5 years after the fundoplication, longer than follow-up periods in most laparoscopic series for GERD.

Patients with anatomically normal or functioning fundoplication developed EAC earlier than patients with a failure. Particularly in the patients facing cancer shortly after fundoplication, the critical steps in carcinogenesis are likely already to have taken place prior to surgery. As shown earlier, the increased oxidative stress or the weakness of esophageal mucosal defense mechanisms in GERD patients are affected to only a small extent by successful fundoplication [17,20]. Some cases of dysplasia, possibly already with EAC, may not have been diagnosed before antireflux surgery. This probably was the case with the three patients developing EAC in <2 years after antireflux surgery (one of them was diagnosed once with dysplasia). EAC can, however, develop also many years even after successful antireflux surgery.

A proposed risk factor for EAC is cholecystectomy [21], which was frequent in our study population: more than one-fourths of the patients who developed EAC had undergone cholecystectomy, compared with an overall rate of 10% among the 19 542 antireflux operations performed in Finland from 1987 to 2006. Over three-quarters of patients developing EAC after fundoplication had BE, and one-third of these also had undergone cholecystectomy. BE therefore seems an important risk factor for post-fundoplication EAC. Our findings are well in line with Lagergren’s nationwide analysis, which found BE in all the seven EAC cases occurring more than 5 years after antireflux surgery [22]. The contribution of BE to the increased risk for EAC even after successful antireflux surgery may derive from mechanisms, such as the lower level of apoptosis in BE [23] or induced proliferation by short acid pulses in BE [24].

The majority of fundoplications in our study were total. Roux-en-Y duodenal diversion with partial gastrectomy and vagotomy has been proposed for patients with long-segment Barrett’s. After a mean follow-up of 7.9 years, regression of BE was reported with no progression to high-grade dysplasia or EAC [25]. For our patients, the EACs after this operation did not develop until an average of 13.5 years postoperatively.

This retrospective population-based cohort includes the highest number of EACs after antireflux surgery reported to date with a long follow-up. Long follow-up times are essential, as EAC can develop very late after antireflux surgery [26]. At a national level, fundoplication — many of which surgeries are performed in small volume, and, thus, by less-experienced units — does not seem to prevent EAC. To achieve a durable antireflux effect, both the surgical treatment and the follow-up of these patients should be concentrated to centers well experienced at antireflux surgery, and with sufficient knowledge and skills for the follow-up. Retrospective studies based on registry data have
limitations, but data on health-resource use in Nordic countries such as Finland are generally considered reliable. The data quality of both the Finnish Cancer Registry and of the National Hospital Discharge Register has earned high respect [18,19]. Because all patients underwent antireflux surgery, the diagnosis of GERD itself is unlikely to be a confounder. Although lack of data limited the estimation of the postoperative anatomic status of fundoplication for 28% of our patients, for 30% fundoplication was objectively functioning.

Antireflux surgery thus does not seem to reduce the need for a long follow-up of GERD patients. Especially, patients with pre-fundoplication BE and endoscopic esophagitis may be in danger of developing postoperative EAC. Even a histologically normal preoperative situation should not lead to a false sense of security.

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Appendix A. Conference discussion

Dr S. Mattioli (Bologna, Italy): Professor Salo provides very important information. We know that the long Barrett, longer than 3 cm, is more likely to be associated with cancer. Do you know the rate of long Barrett in your series? Dr Salo: I don’t know. This is the study of Dr Kaukt, who is undertaking a thesis about esophageal adenocarcinoma under my supervision. As far as I know there was no clear difference between long and short type of Barrett’s esophagus in this retrospective population-based study. However, everybody knows that long Barrett has more risk for cancer than the short segment Barrett.

Dr M. Migliore (Catania, Italy): I have just one question. Do you have data on the length of gastroesophageal reflux symptoms prior to fundoplication? This is because the origin of esophageal adenocarcinoma can be due to the duration of reflux history and not just due to the fundoplication.

Dr Salo: We have no data about the length of GERD symptoms before fundoplication. However as many as 80% of the patients had Barrett’s esophagus and almost 80% had macroscopic esophagitis. This means that the GERD was more severe in the patients who developed cancer after fundoplication.