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The risk of oesophageal adenocarcinoma after gastrectomy for peptic ulcer disease

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ABSTRACT

Background: The influence of bile reflux in the development of oesophageal adenocarcinoma remains controversial. This was tested in a cohort of patients who had undergone gastrectomy, a procedure often entailed by substantial bile reflux.

Methods: A population-based cohort study of patients who had undergone gastrectomy for peptic ulcer disease in 1964–2008 in Sweden. Follow-up for cancer and censoring for death were achieved through linkages to nationwide registries of Cancer and Population, respectively. The number of observed cancer cases in the gastrectomy cohort was divided by the expected number, calculated from the incidence of the entire Swedish population of corresponding age, sex and calendar year. Relative risks were thus presented as standardised incidence ratios with 95% confidence intervals.

Results: After exclusion of all person-years the first year after surgery, the final gastrectomy cohort comprised of 19,767 patients. These patients were followed up for a median of 17 years, and contributed with a total of 348,231 person-years at risk. The observed number of patients with oesophageal adenocarcinoma ($n = 7$) was not higher than the expected ($n = 11.6$), providing a standardised incidence ratio of 0.6 (95% CI 0.2–1.2). There were no clear differences between sexes, age groups or latency intervals after gastrectomy.

Conclusions: Gastrectomy for peptic ulcer disease does not appear to increase the risk of oesophageal adenocarcinoma.

1. Introduction

Oesophageal adenocarcinoma is characterised by a poor prognosis and a rapidly increasing incidence during the last few decades,[1,2] patterns that stress the need for aetiological research. Gastro-oesophageal reflux, causing the premalignant epithelial metaplasia Barrett's oesophagus, is the main risk factor for this tumour.[3] Animal studies have indicated that duodeno-gastro-oesophageal reflux, with high contents of bile in the oesophagus, is an especially harmful component of reflux in the development of oesophageal adenocarcinoma,[4–7] and mechanisms explaining the carcinogenic effects of bile are being explored.[7–9] The association between bile reflux and oesophageal adenocarcinoma in humans has, however, not been established. The slightly increased risk of oesophageal adenocarcinoma reported after cholecystectomy might be caused by an increased presence of bile in the oesophagus,[10] but the average oesophageal bile exposure after cholecystectomy is low. The situation that occurs after partial or total gastrectomy mimics a human experimental model of bile reflux, since such surgery is often followed by a substantially increased risk of oesophageal exposure to bile.[11–19] The

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anatomical rearrangement after gastrectomy means that duodenal contents easily flow back and reach the oesophagus. Data from a case series have suggested an increased risk of oesophageal adenocarcinoma after such surgery.[20] Problems with evaluating risk of oesophageal adenocarcinoma after gastrectomy include the limited number of patients currently treated with such surgery, the need for a long follow-up time to assess cancer risk, and the low incidence of oesophageal adenocarcinoma. In Sweden, there are excellent opportunities for research based on nationwide and complete health care registries with a long history. These sources were utilised to conduct a cohort study assessing the relation between gastrectomy for peptic ulcer disease and risk of developing oesophageal adenocarcinoma.

2. Methods

2.1. Study design

This was a Swedish population-based cohort study, addressing the risk of developing oesophageal adenocarcinoma after gastrectomy, using the entire Swedish population during the study period 1964 through 2008 as database. The study cohort consisted of all patients who had undergone gastrectomy for a peptic ulcer disease during the study period, as recorded in the Swedish Patient Registry. Since there has been no private in-hospital care for patients undergoing gastrectomy in Sweden and patients have been obliged to use a hospital in their county of residence, the study is defined as population-based. The identification of patients developing oesophageal adenocarcinoma was assessed from the Swedish Cancer Registry. The incidence of cancer among the gastrectomy patients was compared with the incidence in the entire Swedish population of corresponding age, sex, and calendar year. Both in the study cohort and in the comparison population only first tumours were included. The first year after gastrectomy was excluded to reduce the risk of detection bias, i.e. earlier detection of any cancer because of the gastrectomy, and to allow a minimum exposure time of exposure. For exclusion of person-time no longer at risk of being identified in the Cancer Registry, the dates of death were collected through linkage to the Swedish Cause of Death Registry. The personal identity number, a 10-digit number assigned to every resident in Sweden since 1947, allowed individual linkages between registries.[21] The study was approved by the Regional Ethical Review Board in Stockholm.

2.2. Exposure data – gastrectomy for benign disease

The patients who underwent gastrectomy for peptic ulcer disease were identified through the Swedish Patient Registry, containing data on all hospitalisations and surgical procedures performed in Sweden since 1964. The Swedish Patient Registry includes data on the patients' age, sex, personal identity number, up to six discharge diagnoses and six surgical procedures, and the dates of each hospitalisation. Sixty percent of the Swedish population was covered by this registry in 1969 and 85% in 1983, and since 1987 the coverage has been 100%. Validation studies of the operation codes in this registry have reported 99% completeness.[22] The diagnosis codes representing peptic ulcer disease were defined by the International Classification of Diseases (ICD) (version 7: 540, 541, 542, 543, 544, and 545; version 8: 531, 532, 533, 534, 535, 536, and 537; version 9: 531, 532, 533, 534, 535, 536, and 537; and version 10: K25, K26, K27, K28, K29, and K31). Among these peptic ulcer patients, the gastrectomy cohort included all patients who had undergone partial or total gastrectomy according to the Patient Registry. The operation codes representing such surgery were defined by the Swedish Classification of Surgical Procedures (edition 5: 4421, 4423, 4439; edition 6: 4411, 4412, 4413, 4414, 4415, 4416, 4417, 4418, 4419, 4420, 4422, 4425, 4426, 4429, 4430, 4432, 4434, and 4435; and edition 7: JDC and JDD).

2.3. Outcome data – oesophageal adenocarcinoma

All cancers diagnosed during follow-up of the cohort were identified through linkage to the Swedish Cancer Registry, a nationwide registry initiated in 1958. This registry contains information about the location, histological type, and date of diagnosis of all malignant tumours in Sweden. The codes for all tumour diagnoses are converted into the ICD codes version 7, and oesophageal adenocarcinoma was defined by the code 1500 for oesophageal cancer combined with the histological code 096 for adenocarcinoma. Other key variables of the Cancer Registry include the personal identity numbers, age and sex. A validation study regarding oesophageal cancer registration of the Cancer Registry found a completeness rate of 98%.[23]

2.4. Statistical analyses

Person-time at risk was accumulated from one year after the surgery until the first occurrence of any cancer, death or the end of observation (31st December 2008), whichever came first. The relative risk was estimated as the standardised incidence ratio (SIR), i.e. the number of oesophageal adenocarcinomas in the gastrectomy cohort (observed number of cases) divided by the number of oesophageal adenocarcinomas in the comparison population (expected number of cases). The expected number of cancers was calculated by multiplying the observed person-time by cancer incidence rates specific for age, sex and calendar year. The expected rates were derived from the Swedish Cancer Registry data through the Swedish population and aggregated into 5-year intervals. Confidence intervals (CIs) of SIRs were calculated on the assumption that the observed number of events followed a Poisson distribution.[24] The SIRs were inherently adjusted for the potential confounding factors age, sex and calendar year, as the incidence in the observed cohort was compared with the corresponding incidence in the age-, sex- and calendar year-matched general population. The Statistical Analysis System (SAS), version 9.2, SAS Institute Inc., Gary, North Carolina, USA, was used for all analyses.

3. Results

The gastrectomy cohort included 19,767 patients. Some characteristics of this cohort are presented in Table 1. The cohort members were followed up for a median of 17 years, and the

Table 1 – Characteristics of the 19,767 study patients who underwent gastric resection in Sweden during the period 1964–2008.

Variable	Men	Women	All
Individuals, number (%)	12 391 (62,7)	7 376 (37,3)	19 767
Person-years, number (%)	213 846 (63.9)	120 773 (36.1)	334 619
Age at entry, median years	57	60	58
Calendar year of entry, median	1976	1980	1978
Follow-up time, median years	17	16	17
Type of surgery, number (%)			
Partial gastrectomy	11 986 (96.7)	7 061 (95.7)	19 047 (96.4)
Total gastrectomy	405 (3.3)	315 (4.3)	720 (3.6)

total number of person-years at risk was 348,231. The study cohort consisted of more men (62.3%) than women. The vast majority of operations were partial gastrectomies (96.4%), while the remaining part was total gastrectomies.

The observed number of patients who developed oesophageal adenocarcinoma during follow-up was 7, which was slightly less than the expected number, providing a standardised incidence ratio of 0.6 (95% CI 0.2–1.2). There were no strong differences between sexes, age groups or periods of latency time after the gastrectomy (Table 2).

4. Discussion

This study does not provide any evidence in support of the hypothesis that gastrectomy increases the risk of oesophageal adenocarcinoma.

Advantages of the study include the population-based cohort design, the complete assessment of both the exposure and the outcome, and the long follow-up period. The use of a gastrectomy cohort could be regarded as a human experiment model that allows assessment of effects of the exposure to bile reflux. A limitation is the low number of incident patients diagnosed with oesophageal adenocarcinoma in the cohort. Despite the large cohort size and the length of the follow-up, the low incidence of oesophageal adenocarcinoma reduced the statistical power. The study was however convincingly negative from a power perspective, since the upper border of the confidence interval was only 1.2. The study provided limited possibilities to adjust for potential confounding. Adjustments for age, sex, and calendar year, however, were done through the design. Among other established risk factors for oesophageal adenocarcinoma, i.e. gastroesophageal reflux, obesity and tobacco smoking,[25] reflux should not be adjusted for since it lies in the hypothesised causal pathway.[26] Moreover, it is unlikely that negative confounding by obesity or tobacco smoking would explain the lack of association. Tobacco smoking is rather associated with an increased risk of ulcer disease, which was supported by an increased risk of lung cancer in this gastrectomy cohort (SIR 2.4, 95% CI 2.2–2.6).

This is the first cohort study addressing the relation between gastrectomy for peptic ulcer disease and the risk of developing oesophageal adenocarcinoma. Previous research addressing the direct relation between gastrectomy and oesophageal adenocarcinoma consists of case series. In a follow-up of a series of 155 patients with Barrett's oesophagus aimed to address the risk of oesophageal adenocarcinoma, by coincidence, all four identified cases of oesophageal adenocarcinoma had previously undergone gastric surgery, against 40 in the total series.[20] In another case series, the rate of previous gastric resections was similar among patients with oesophageal adenocarcinoma (4 out of 325 = 1%) and oesophageal squamous cell carcinoma (1 out of 117 = 1%).[27] In a case-control study addressing a surrogate marker of oesophageal adenocarcinoma, Barrett's oesophagus, a history of gastrectomy was equally common among patients with Barrett's oesophagus (40 out of 1016 = 4%) as among the control participants (162 out of 3047 = 5%), rendering no increased relative risk.[28] To summarise the results of the present study with the available previous research, there is not much support for an association between gastrectomy and oesophageal adenocarcinoma, why the critical role of bile

Table 2 – Standardised incidence ratios (SIR) and 95% confidence intervals (CIs) of oesophageal adenocarcinoma in a gastric resection cohort, consisting of 19,767 patients in Sweden during the period 1964–2008.

	Observed cases	Expected cases	SIR	95% CI
All	7	11.6	0.6	0.2–1.2
Sex				
Male	5	10.2	0.5	0.2–1.1
Female	2	1.4	1.4	0.2–5.2
Age				
<70 years	3	3.8	0.8	0.2–2.3
⩾70 years	4	7.8	0.5	0.1–1.3
Latency after gastrectomy				
1–20 years	3	6.6	0.5	0.1–1.3
21–43 years	4	5.0	0.8	0.2–2.0

reflux in the aetiology of this tumour in humans must be questioned.

In conclusion, this population-based and nationwide Swedish cohort study with long-term follow-up of a large gastrectomy cohort does not support the hypothesis that gastrectomy increases the risk of oesophageal adenocarcinoma.

Author contribution

Jesper Lagergren was responsible for the study concept and design, acquisition and interpretation of data, drafting of the manuscript. Anna Lindam was responsible for the statistical analysis, and provided critical revision of the manuscript.

Responsibility statement

The corresponding author had full access to all of the data and takes full responsibility for the veracity of the data and statistical analysis.

Conflict of interest statement

None declared.

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