OESOPHAGEAL CANCER:

ON SURGERY AND AETIOLOGY

Martin Rutegård

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TILL TOMAS – I LJUST MINNE BEVARAD
ABSTRACT

Oesophageal cancer is a common type of cancer with a dire prognosis. It is globally the eight most frequent malignancy and the sixth leading cause of death from cancer. The doctoral research described in this thesis has addressed the surgical treatment of oesophageal cancer from a morbidity perspective. It also provides some insight into the enigmatic male predominance of the most rapidly increasing subtype of oesophageal cancer, namely adenocarcinoma.

In the first study, the association between surgical factors and health-related quality of life was evaluated on the basis of data from a nationwide surgical register, comprising 355 surgically treated patients. A clinically relevant, statistically significant deterioration in several aspects of functioning and symptoms 6 months after surgery was shown in patients suffering from postoperative surgical complications.

The second study was based on the same research register with the same patients and concerned the relation of hospital and surgeon volume to health-related quality of life 6 months after surgery. No influence of surgical volume on the patients' functioning and symptoms was discerned.

In the third study the same surgical register was again used, but virtually all the patients who underwent oesophageal resection for cancer in Sweden from 2001 to 2005, inclusive, were involved. This prospective cohort study of 615 patients addressed the relationship between surgeon volume and postoperative surgical complications within 30 days. Surgeon volume had no discernible effect on the risk of surgical complications. Individual high-volume surgeons proved to have greatly differing results.

The fourth study was based on data from the Swedish Cancer Register and the Total Population Register. In this retrospective study the age-dependency of the incidence ratio of male to female gastrointestinal adenocarcinoma was evaluated. The sex ratio in oesophageal adenocarcinoma proved to be strikingly age-dependent, with point estimates of 8:10:1 in the younger age groups and about 4:1 in the older ones. This decline seemed to be steady and not related to the time of menopause in women, thus questioning the potential influence of oestrogen on the development of oesophageal adenocarcinoma.

The fifth and last study was based on a randomly selected sample from the adult Swedish population, comprising 4906 participants. This cross-sectional study strove to investigate the sex distribution of the established risk factors for oesophageal adenocarcinoma in the general population. Individual risk factors such as high BMI, tobacco smoking, and non-use of NSAIDs were overrepresented in men, while gastro-oesophageal reflux was more prevalent in women. No apparent clustering of risk factors was observed in men, and differences in separate risk factor exposure were small.

Keywords: oesophagus, neoplasm, health-related quality of life, surgery volume, population-based, adenocarcinoma, sex ratio, risk factors.
LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals (I-V).

I. Martin Rutegård, Jesper Lagergren, Ioannis Rouvelas, Mats Lindblad, Jane Blazeby, Pernilla Lagergen. 
Population-based study of surgical factors in relation to health-related quality of life after oesophageal cancer resection. 

II. Martin Rutegård, Pernilla Lagergren. 
No influence of surgical volume on health-related quality of life six months after esophageal cancer resection. 

III. Martin Rutegård, Ioannis Rouvelas, Jesper Lagergren, Pernilla Lagergren. 
Surgeon volume is a poor proxy for skill in esophageal cancer surgery. 
Annals of Surgery 2009; 249: 256-261

IV. Martin Rutegård, Richard Shore, Yunxia Lu, Pernilla Lagergren, Mats Lindblad. 

V. Martin Rutegård, Helena Nordenstedt, Yunxia Lu, Jesper Lagergren, Pernilla Lagergren. 
Male predominance in oesophageal adenocarcinoma is not explained by sex differences in exposure prevalence of established risk factors. 
Submitted.

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LIST OF ABBREVIATIONS

CI Confidence interval
CT Computerised tomography
EORTC European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30 EORTC Quality of Life Questionnaire – Core 30
EORTC QLQ-OES18 EORTC Quality of Life Questionnaire – Oesophageal 18

H. pylori *Helicobacter pylori*
HVH High-volume hospital
HVS High-volume surgeon
HRQL Health-related quality of life
LVH Low-volume hospital
LVS Low-volume surgeon
MVS Medium-volume surgeon
NSAID Non-steroidal anti-inflammatory drug
OR Odds ratio
PET Positron emission tomography
RP Reference Population (study)
SECC Swedish Esophageal and Cardia Cancer (register)
TNM Tumour-node-metastasis (classification system)
INTRODUCTION

Cancer localised to the oesophagus, including the oesophago-gastric junction, is relatively uncommon from a European perspective\(^1\) and in the year 2008 the number of cases of oesophageal cancers in Sweden was 396 and the number of cases of cancer of the gastric cardia was 198.\(^2\) Nevertheless, oesophageal cancer is the eighth most frequent cancer worldwide and the sixth most common cause of death from cancer.\(^3\)

Although there is considerable controversy in the literature,\(^4\) in this thesis the term oesophageal cancer will hereafter be used to refer to cancer in the oesophagus as well as in the gastric cardia, unless otherwise stated, as the epidemiology and treatment of both entities more often than not coincide.\(^5\)

Oesophageal cancer is an aggressive disease and the five-year survival rate is below 16% in the Western world.\(^3\) As this cancer rarely becomes symptomatic in the early stages, most patients present with advanced disease at diagnosis.\(^6\) In patients with a localised tumour, surgical resection is the mainstay of treatment, often complemented by neoadjuvant chemoradiotherapy.\(^7\) Oesophagectomy for cancer typically involves extensive surgery of the abdomen and the chest, while a neck dissection sometimes is added, and the postoperative mortality and morbidity are considerable.\(^7\)-\(^9\) Nevertheless, advances in non-invasive imaging, preoperative staging, anaesthesia and the surgical technique, as well as in postoperative care, have reduced the in-hospital operative mortality to below 5% in experienced centres.\(^8\)-\(^10\) Similarly, the long-term survival rates have improved, although still fewer than 40% of patients with a radical resection are considered cured.\(^6\),\(^7\) Morbidity is still a major concern in oesophageal cancer surgery, with perioperative complication rates ranging from 26-41%.\(^6\) As the prognosis for oesophagectomised patients remains so bleak despite recent advances, increasing interest is being focused on attempts to reduce morbidity and improve longstanding symptoms and persisting low function in these patients. Current research indicates that oesophagectomy has a major impact on these measures of health-related quality of life (HRQL) both in the short and in the long term, but few studies have addressed the influence of surgical technique in this respect.\(^11\),\(^12\)

The epidemiology of oesophageal cancer is marked by striking differences worldwide in the incidence, morphology and aetiological agents: 20-fold variations in incidence have been found between high-risk China and low-risk western Africa, and the vast majority of cancers in the developing world are squamous cell carcinomas, mostly caused by environmental exposures.\(^3\) In contrast, the Western world has witnessed a major epidemiological shift in recent decades, where the formerly all but unknown adenocarcinoma type of cancer has
surpassed squamous cell carcinoma in incidence, especially among white males.\textsuperscript{13, 14} While major risk factors such as gastro-oesophageal reflux disease\textsuperscript{15} and overweight\textsuperscript{16} have been identified, there is still much uncertainty as to whether the concurrent epidemic in obesity and associated reflux disease might adequately explain the unprecedented rise in the incidence of oesophageal adenocarcinoma. Moreover, the conspicuous male-to-female ratio of 7-10 to 1 in worldwide oesophageal adenocarcinoma incidence\textsuperscript{17} does not seem to be explained by differences in risk factor exposure,\textsuperscript{18, 19} thus further adding to the enigma of oesophageal adenocarcinoma.

This thesis, based on three original papers on the surgical treatment of oesophageal cancer and two papers on the male preponderance in oesophageal adenocarcinoma, attempts to identify causes of low functioning and symptoms in surgically treated patients as well as to shed some light on the aetiological puzzle of oesophageal adenocarcinoma. By increasing the knowledge of how surgery affects patient morbidity, contributions could hopefully be made to improve the treatment of these patients. With more information on the sex differences in incidence and risk factors of oesophageal adenocarcinoma, future research could potentially pave the way for new preventive measures and new alternative treatment options.
BACKGROUND

OVERVIEW OF ANATOMY AND TUMOUR BIOLOGY

The oesophagus

The term oesophagus originates from the Greek oisophágos, created from oisein (derivative of phérein, "to carry") and phagos ("to eat").

The oesophagus is a midline tubular structure situated mainly in the thoracic cage, anterior to the spine and posterior to the trachea. It originates at the cricoid cartilage in the neck, runs caudally in the posterior mediastinum and terminates in the abdomen at the oesophago-gastric junction (Fig. 1). Measuring from the incisor teeth, the distance to the tracheal bifurcation is from 23 to 26 cm, and to the gastric opening 39 to 48 cm. The oesophagus is divided topographically into three parts: cervical, thoracic, and abdominal. The tissue organisation of the oesophagus parallels the basic plan of the gastrointestinal system, comprising a mucosa of squamous epithelium, a submucosa with extended lymphatics, a muscular layer with striated muscle proximally and smooth muscle distally, and finally an adventitial layer; however, it lacks a serosal coating until the oesophago-gastric junction is reached.

Figure 1. The oesophagus and its anatomical relations. A: Anterior view. B: Left lateral view. The artwork is reproduced, with permission, from the Johns Hopkins Gastroenterology and Hepatology Resource Center, www.hopkins-gi.org, copyright 2009, Johns Hopkins University, all rights reserved.
Carcinogenesis

As postulated by Nowell in 1976, cancer develops as a multistep process involving increased instability of the genome. Genetic changes in some cells imply a selective proliferative advantage, providing a basis for clonal expansion and a further increase in instability, with a risk of multiple genetic changes and finally loss of proliferative control and development of invasive capabilities.\textsuperscript{22}

\textbf{Figure 2.} Endoscopic view of early adenocarcinoma in Barrett's oesophagus. The artwork is reproduced, with permission, from the Johns Hopkins Gastroenterology and Hepatology Resource Center, www.hopkins-gi.org, copyright 2009, Johns Hopkins University, all rights reserved.

In the setting of oesophageal adenocarcinoma, most research indicates that repeated mucosal injury inflicted by gastro-oesophageal reflux aggravates the progression of intestinal metaplasia. This was first described in 1950 and the term Barrett's oesophagus was coined, defined as the replacement of the normal squamous mucosa with a columnar epithelium.\textsuperscript{23} It has been postulated that this ectopic columnar epithelium predisposes the patient to dysplasia and ultimately adenocarcinoma, thus establishing a carcinoma sequence. Barrett's oesophagus is indeed considered a premalignant condition, with a 30- to 100-fold increase in the risk of developing adenocarcinoma as compared to the general population.\textsuperscript{24, 25} This progression from metaplasia to dysplasia to adenocarcinoma has also been observed in patients under endoscopic surveillance, but it is important to note that the risk per year of developing adenocarcinoma is only 0.6% in patients with
documented Barrett's oesophagus and that the vast majority of patients with Barrett's oesophagus will die of another cause than oesophageal adenocarcinoma. A current view on adenocarcinoma development is summarised in Figure 3, where the main risk factors (obesity, reflux disease, and tobacco smoking) and the pathways leading to cancer are depicted (see section on epidemiology for details on risk factors).

**Figure 3.** A proposed pathway for oesophageal adenocarcinogenesis.

Epidemiological evidence points to the possibility that obesity, specifically of the abdominal type, may cause adenocarcinoma independent of reflux disease. The major mechanism by which obesity might cause cancer was previously thought to be through increased intragastric pressure and induction of reflux disease, but there is little evidence supporting this notion. Rather, awareness has increased that central and peripheral fat exhibit different activity, e.g. in hormonal production, which may influence both reflux disease and systemic targets.

Squamous cell carcinoma of the oesophagus has a less well documented carcinoma sequence, but occurs frequently as a consequence of chronic mucosal irritation, induced by exposure to tobacco, alcohol or dietary factors.

**Classification of the oesophago-gastric junction**

Considerable controversy and uncertainty exists in the literature concerning the classification of tumours related to the oesophago-gastric junction. The junction itself is defined differently by anatomists, physiologists, endoscopists and pathologists and the confusion of how to adequately discriminate the gastric cardia from the distal oesophagus and the proximal stomach has muddled the waters of surgical management as well as the epidemiology of the oesophago-gastric junction tumours. The relatively recently introduced Siewert classification has become generally accepted: here oesophago-gastric tumours are as a whole defined as tumours whose centres are located within 5 cm proximal and 5 cm distal to the oesophago-gastric junction. Furthermore, three subgroups are defined, as follows: Type I, adenocarcinoma of the distal oesophagus more than 1 cm above the oesophago-gastric junction; Type II, true gastric cardia adenocarcinoma located within 1 cm proximal and 2 cm distal to the junction; Type III, subcardiac gastric carcinoma with the tumour mass more than
2 cm distal to the junction and invading the junction and possibly the distal oesophagus from below. This classification, although widespread, has the inherent limitation of being based on anatomical landmarks that may well be obscured by tumour growth; furthermore, there is no apparent biological rationale for the proposed definition.

**OESOPHAGEAL CANCER EPIDEMIOLOGY**

The collective term oesophageal cancer refers to several histological types of cancer, but over 90% of the cases comprise squamous cell carcinoma or adenocarcinoma. Oesophageal cancer in developing countries has been dominated by squamous cell carcinoma. Associated with long-recognised risk factors such as smoking and alcohol, this cancer type has declined slightly in the industrialised world in recent decades. Adenocarcinoma, on the contrary, has seen an unprecedented rise in incidence, especially in white men in industrialised countries. Epidemiological studies have disclosed gastro-oesophageal reflux disease and obesity as major risk factors, but the striking male predominance in oesophageal adenocarcinoma has yet to be explained.

**Oesophageal adenocarcinoma**

**Incidence and trends**

In most parts of the Western world, the incidence of oesophageal adenocarcinoma has been consistently rising over the past four decades, with few signs of abating. Sweden is no exception, as shown in Figure 5. Importantly, this incidence rise has affected men and women in unequal proportions, where the rise in the latter has been more modest. Furthermore, there are major differences in incidence from a geographical perspective, the white populations in the United Kingdom and Ireland, United States and Australia displaying the highest figures, whereas Europe in general has half the incidence and Asia exhibits only about a tenth as much.
Aetiology

Gastro-oesophageal reflux disease

Symptomatic gastro-oesophageal reflux disease is the strongest established risk factor for oesophageal adenocarcinoma, as shown by population-based studies revealing fivefold or higher relative risks.\textsuperscript{15, 34, 35} This risk is also decidedly higher in those who suffer from more frequent, severe and longstanding reflux disease,\textsuperscript{15, 34, 35} and might be over 40 times higher in these individuals compared to unaffected persons.\textsuperscript{15} Reflux disease in itself is common, affecting 10-20\% of the general population.\textsuperscript{36} Onset of the cardinal symptoms, heartburn and acid regurgitation, usually occurs in middle age.\textsuperscript{37} Despite the elevated risk in these persons, it is of importance to note that reflux disease is infrequent or absent in 40-48\% of people who develop oesophageal adenocarcinoma.\textsuperscript{15, 35} Further, the prevalence of intestinal metaplasia in the general population is only 2.3\% in those reporting reflux symptoms, compared to 1.2\% in those who do not.\textsuperscript{38}

Obesity

During the last decades there has been such a rapid increase in the prevalence of overweight and obesity, not only in the Western world but also in middle-income countries such as India and China, that it is called a new global epidemic.\textsuperscript{39-41} As measured by body mass index (BMI), obesity clearly increases the risk of oesophageal adenocarcinoma\textsuperscript{16, 18, 34, 42, 43} and recent meta-analyses have concluded that there is a dose-response relationship, with an almost doubled risk in overweight and an even higher risk in obese individuals.\textsuperscript{44, 45}
In recent years it has been proposed that the increased risk of adenocarcinoma in association with obesity is to a large extent attributable to the distribution of fat tissue; this is based on studies on the precursor lesion Barrett's oesophagus. In a retrospective case-control study in which visceral fat was ascertained by computerised tomography (CT), the positive association of BMI with intestinal metaplasia disappeared when adjustment was made for adipose tissue content, which in itself was strongly linked to the condition.\textsuperscript{46} Corroborating these results, a high waist-to-hip ratio was found to be strongly associated with intestinal metaplasia, even after adjustment for BMI and potential confounders such as reflux and smoking.\textsuperscript{47} Similar results were shown with use of waist circumference in a larger, community-based, study.\textsuperscript{48} Using the same cohort, abdominal diameter was also found to increase adenocarcinoma risk independently.\textsuperscript{42}

\textit{Alcohol intake and tobacco smoking}

Population-based studies have shown no increase in the risk of oesophageal adenocarcinoma in connection with alcohol consumption,\textsuperscript{49, 50} whereas cigarette smoking seems to approximately double the risk.\textsuperscript{18, 34, 51}

\textit{Non-steroidal anti-inflammatory drugs}

Numerous studies and meta-analyses have shown an inverse association between the use of NSAIDs (including aspirin) and oesophageal adenocarcinoma,\textsuperscript{52-56} although these studies may have been limited by selection bias and confounding by indication (or contraindication).\textsuperscript{57} Conflicting results have surfaced when adjustment for contraindication, i.e. upper gastrointestinal disorders where NSAID use is discouraged, has been made.\textsuperscript{58, 59} Patients with Barrett's oesophagus\textsuperscript{60} or chromosomal instability\textsuperscript{61} do seem to benefit from NSAID use concerning risk of adenocarcinoma development, but a recent randomised trial in which the use of celecoxib (a selective NSAID) was evaluated failed to discern any preventive effects on progression to cancer.\textsuperscript{62}

\textit{Helicobacter pylori}

A link between \textit{Helicobacter pylori} (\textit{H. pylori}) infection and oesophageal adenocarcinoma has been suggested, as the prevalence of \textit{H. pylori} infection has fallen during a period of increasing oesophageal adenocarcinoma incidence. Moreover, such infection could influence the contents of the gastric juice by reducing the acidity by causing atrophic gastritis. A few studies have indeed found a protective effect of \textit{H. pylori} infection, as measured by serum markers or bacteria prevalence, on the adenocarcinoma risk\textsuperscript{63-65}; although evidence is conflicting,\textsuperscript{63, 64} at least some of the risk reduction might be caused by gastric atrophy.\textsuperscript{65} A recent meta-analysis concluded that the adenocarcinoma risk is halved with signs of infection,\textsuperscript{66} though causality is not established. Intriguingly, there is evidence that the pattern of gastric colonisation plays an important role. The risk of
adenocarcinoma may in fact be increased in duodenal ulcer patients, in whom the *H. pylori* infection is confined to the antrum and induces hyperchlorhydria.67

**Dietary factors and socioeconomic status**

A diet low in fibre, fruit and vegetables seems to increase the risk of oesophageal adenocarcinoma,68-71 which is also increased by a diet high in total fat and cholesterol.71 Moreover, a low socioeconomic status as measured by few years of education and low income increases the risk.51,72

**Heredity**

Two population-based studies have been conducted in Sweden, with conflicting results: in a case-control study, no increase in the risk of adenocarcinoma was found in first-degree relatives of patients with oesophageal cancer,73 whereas register-based cohort data indicated a slightly elevated risk.74 Taken together, heredity seems to play a limited role.

**Gastric cardia adenocarcinoma**

The incidence of gastric cardia cancer is difficult to appreciate, as misclassification issues make comparisons contentious. However, it seems that the incidence has been rising in the developed countries along with the increase in oesophageal adenocarcinoma, but to a more moderate extent.75 In Sweden, this rise has stabilised and the incidence might even be on the decline, as shown in Figure 6.2

![Gastric Cardia Adenocarcinoma](image)

**Figure 6.** Age-standardised incidence of gastric cardia adenocarcinoma per 100,000, stratified by sex, in Sweden from 1970 to 2008 inclusive.
The strong association between oesophageal adenocarcinoma and established risk factors such as gastro-oesophageal reflux disease and obesity is mitigated in adenocarcinoma of the gastric cardia. Smoking seems to be equally harmful at both locations, if not more so in the gastric cardia, whereas the preventive effect of NSAID use has not been proven for gastric cardia adenocarcinoma. The relation to *H. pylori* is disputed, as also are findings on molecular differences. There is evidence of familial clustering in gastric cardia and oesophageal adenocarcinoma, where the risk of cardia cancer is substantially increased when oesophageal adenocarcinoma is present in relatives.

The above findings might be interpreted as a reason to discriminate between gastric cardia adenocarcinoma and adenocarcinoma of the distal oesophagus from an aetiological perspective, but they may also be a product of misclassification in cancer registries, especially since not all epidemiological studies use the same classification of the oesophago-gastric junction and its tumours. Furthermore, in a population-based study of gastric cardia and oesophageal adenocarcinomas from the UK, it was suggested that these cancers share epidemiological, aetiological and clinico-pathological features to such an extent as to warrant the conclusion that they are the same disease, albeit at slightly different locations. By contrast, an evaluation of US birth cohorts indicating that the rise in incidence of oesophago-gastric tumours is indeed confined to oesophageal adenocarcinoma would suggest that these entities need to be studied in isolation. Moreover, it has been postulated that gastric cardia cancer has in fact at least two different aetiologies, of which the first is an association with gastric atrophy, while the other is reflux.

To conclude this section, there is considerable controversy regarding the extent to which gastric cardia and oesophageal adenocarcinoma should be treated as common entities, and much more research is needed to elucidate potential differences between the Siewert types concerning tumour biology and epidemiology.
Squamous cell carcinoma

Incidence and trends

The incidence of oesophageal squamous cell carcinoma is decreasing in most industrialised countries, while it is still a matter of major concern in other parts of the world.32, 33 Sweden is no exception, as shown in Figure 7.2

![Oesophageal Squamous Cell Carcinoma](image)

**Figure 7.** Age-standardised incidence in oesophageal squamous cell carcinoma per 100,000, stratified by sex, in Sweden from 1970 to 2008 inclusive.

Aetiology

**Alcohol intake and tobacco smoking**

Tobacco smoking and high alcohol consumption are major risk factors for oesophageal squamous cell carcinoma in the developed world,51, 81 which may explain the male predominance and the decline in incidence, which has been attributed to smoking reduction.32 The combination of these risk factors confers even higher risks,50 and may account for up to 90% of the squamous cell carcinomas in the industrialised world.6

**Dietary factors and socioeconomic status**

A low intake of fruit and vegetables82 is associated with a higher risk, as also are deprivation and a low socioeconomic status.72 The ever rarer Plummer-Vinson deficiency syndrome, associated with an inadequate nutritional status, is also a
risk factor when present.\textsuperscript{83}

\textit{Heredity}

Although population-based studies have not shown any risk increase associated with heredity,\textsuperscript{73, 76} there is a familial syndrome, tylosis, which confers a strikingly high risk for squamous cell carcinoma.\textsuperscript{84}

\textit{Other}

Chronic irritation is potentially carcinogenic for the squamous epithelium, and associations with cancer development have been found in conditions prone to mucosal damage such as achalasia,\textsuperscript{85, 86} intake of hot beverages\textsuperscript{87} and caustic injury of the oesophagus.\textsuperscript{88, 89}

\section*{OESOPHAGEAL CANCER AND SURGERY}

Even though various approaches and slightly different modalities of treatment are described in the literature for the different types of oesophageal cancer such as distal adenocarcinoma, gastric cardia adenocarcinoma and the often more proximally located squamous cell carcinoma, the bulk of the surgical research to date has dealt with these cancer types collectively.\textsuperscript{90} Most of the debate has revolved around the treatment of true gastric cardia adenocarcinoma.\textsuperscript{91, 92} However, most centres prefer to treat distal adenocarcinomas, including Siewert type I, and the type II cancer, by oesophagectomy and manage the type III cancers along gastric carcinoma guidelines, as evidence indicates that lymphatic drainage and recurrence patterns as well as survival are similar for type I and II cancers.\textsuperscript{91}

This section concerning oesophageal cancer treatment will therefore not discriminate between the tumour types, unless otherwise indicated. Important differences will nevertheless be mentioned.

\section*{Historical and current perspective}

The first successful resection for oesophageal cancer took place in 1913. For the better part of the last century, oesophagectomy was considered an almost suicidal procedure with appalling mortality rates in its wake, despite the fact that surgery proved to be the only hope as definitive treatment.\textsuperscript{93} Postoperative mortality has since then been declining consistently along with advances in non-invasive imaging, preoperative staging, anaesthesia and the surgical technique, as well as postoperative care.\textsuperscript{7} Recent decades have still seen slight improvements in survival, but further refinements in the surgical technique are not expected to influence the prognosis significantly. The research focus in oesophageal cancer surgery has therefore shifted from mortality to morbidity, as evidenced by the
investigations on complications and postoperative HRQL, with attempts to lend life to the years left in the majority of patients.\textsuperscript{11, 12, 94-96}

\section*{From diagnosis to surgery}

\subsection*{Symptoms}

Oesophageal cancer is an insidious disease, and the patient typically presents with dysphagia due to luminal obstruction, at the point where the disease has systemically spread in a majority of patients.\textsuperscript{6, 97} The next most frequent symptom is weight loss, followed by heartburn, odynophagia and dyspnoea.\textsuperscript{97} The latter, together with cough, hoarseness and retrosternal, back or right upper abdominal pain, is suggestive of metastatic disease; this is also indicated by hepatomegaly and presence of a Virchow's node.\textsuperscript{6}

\subsection*{Diagnosis and staging}

Flexible upper endoscopy is the primary mode of investigation in suspected oesophageal cancer. A macroscopic evaluation and a histological diagnosis are both possible, the latter through biopsies. In order to decide upon the management and individualise treatment, staging of the disease using the tumour-node-metastasis (TNM) classification system\textsuperscript{98} is necessary. Further investigations are performed to assess the depth of wall invasion (T), the extent of lymph node involvement (N) and the occurrence of distant metastasis (M). Depending on the severity of the disease as reflected by these parameters, oesophageal cancer is grouped into categories, where stage I represents the mildest form and stage IV the most severe (Table 1).

CT of the chest, abdomen and pelvis is standard practice to evaluate the possibility of distant metastasis.\textsuperscript{6} More recently, positron emission tomography (PET) has been introduced to more accurately assess early distal spread\textsuperscript{99} and some centres employ both in a combined CT-PET approach, thus enhancing the CT scan's sensitivity as well as allowing better localisation of any metastases indicated by the PET findings.\textsuperscript{100} Barring the presence of distant metastasis, endoscopic ultrasonography is chiefly performed to assess local tumour depth and regional lymph node involvement, for which the sensitivity is superior to that of CT alone.\textsuperscript{100} When combined with fine-needle aspiration and cytological diagnosis of any suspicious lymph nodes, the sensitivity and specificity are improved.\textsuperscript{101} Finally, thoracoscopic and laparoscopic staging claim high accuracy for detection of metastases, particularly of early tumour seeding, but apart from being invasive, these procedures do not alter the management for more than a fraction of the patients and are therefore not in widespread use.\textsuperscript{102}
**Table 1.** The 2002 American Joint Committee on Cancer (AJCC) staging system for oesophageal cancer.

**Definition of TNM**

*Primary tumour (T)*
- **TX**: Primary tumour cannot be assessed
- **T0**: No evidence of primary tumour
- **Tis**: Carcinoma in situ
- **T1**: Tumour invades lamina propria or submucosa
- **T2**: Tumour invades muscularis propria
- **T3**: Tumour invades adventitia
- **T4**: Tumour invades adjacent structures

*Regional lymph nodes (N)*
- **NX**: Regional lymph nodes cannot be assessed
- **N0**: No regional lymph node metastasis
- **N1**: Regional lymph node metastasis

*Distant metastasis (M)*
- **MX**: Distant metastasis cannot be assessed
- **M0**: No distant metastasis
- **M1**: Distant

Tumours of the lower thoracic oesophagus:
- **M1a**: Metastasis in coeliac lymph nodes
- **M1b**: Other distant metastasis

Tumours of the mid-thoracic oesophagus:
- **M1a**: Not applicable
- **M1b**: Non-regional lymph nodes and/or other distant metastasis

Tumours of the upper thoracic oesophagus:
- **M1a**: Metastasis in cervical nodes
- **M1b**: Other distant metastasis

**Stage grouping**

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The above staging procedures, along with other physiological evaluations such as spirometry and bicycle ergometry, are used to evaluate the feasibility of successful surgery – in the end, less than a third of the patients are eligible for resection in population-based settings.103, 104

Prognosis

The overall five-year survival rate for oesophageal cancer patients is below 16% in the Western world.3 The outlook for successfully resected patients is admittedly better, although still fewer than 40% of those patients are considered cured.6, 7 In a Swedish population-based study a stage-specific 5-year survival rate of 63% for stage I cancer was found, 29% for stage II, 9% for stage III and 13% for stage IV; the same study also indicated an improvement in overall survival rates in resected patients from 20% in 1987-91 to 31% in 1997-2000, a statistically significant difference attributed to better patient selection and advances in the surgical technique.105

Surgical treatment

The goal in resection for cancer is to cure the patient at an acceptable cost. To provide increased survival and prevent local recurrence, it is generally accepted that a macroscopically and microscopically radical resection is of the utmost importance.106 Even in radically resected patients, there is evidence that a 5 cm gross tumour margin is necessary to improve survival.107 The limited survival among resected patients is explained by occult local and distal spread that has already occurred at the time of operation, facilitated by the extensive lymphatic network in the oesophageal structural layers.21 Therefore, surgeons have advocated radically different approaches to oesophageal tumours, reflecting the opposing views that this type of cancer is too often systemic at its onset and is hence impossible to cure by extensive surgery, or that it is possible to decrease local recurrence rates and even distal spread by more radical surgery. Numerous surgical approaches are available, but the two most common ones will be described below.

Transthoracic versus transhiatal oesophagectomy

Transthoracic oesophagectomy was first described by Ivor Lewis in 1946.108 It is performed through an upper abdominal incision and a right postero-lateral thoracotomy with an oesophago-gastric anastomosis in the upper thorax. Advocated by most surgeons, this procedure is claimed to offer superior access to the thoracic cavity, which makes an extensive en bloc resection possible, where the tumour-bearing oesophagus within an envelope of adjoining lymphovascular tissue is removed, at times including even the pleural surfaces and the anterior pericardium.109 The rationale for this approach is to minimise tumour spillage and ensure complete removal of the cancer with good margins. In contrast, transhiatal oesophagectomy, which was rediscovered and advocated by Orringer,110 is based
on the concept of incurring as little damage as possible to the patient while still oncologically adequate. Accomplished with an upper abdominal and a cervical incision, the oesophagus is bluntly dissected from above and below.

A thoracotomy is thus avoided and a cervical anastomosis is fashioned. Proponents of the transhiatal approach claim that this procedure is less prone to dangerous complications such as mediastinitis followed by anastomotic leaks and avoids the respiratory complications and postoperative pain associated with thoracotomy. Irrespective of the surgical approach, the most commonly used substitute for the removed oesophagus is the tubularised stomach, although the colon or the jejunum is sometimes used.

The notion that a transthoracic approach is oncologically superior has been hard to prove. In the best designed and powered randomised clinical trial to date, an extensive transthoracic en bloc oesophagectomy was compared with a limited transhiatal operation in patients with adenocarcinoma of the distal oesophagus and the gastric cardia. Pulmonary complications and chylothorax were significantly more common in transthoracically resected patients, but the postoperative mortality was similar in the two groups. In the long-term follow-up, no difference in 5-year survival was noted in the aggregate group, while a survival advantage was discerned for the extended transthoracic approach in type I cardia cancer with a limited number of positive lymph nodes. Partly corroborating these results, a recent large population-based study indicated that the adjusted long-term survival was equal in the two groups.

**Lymph node dissection**

Only one randomised clinical trial has addressed the potential oncological benefit of extending the standard mediastinal and abdominal lymphadenectomy to include cervical lymph nodes; here it was not proven that survival was improved and considerable morbidity was added. There is some observational evidence, however, suggesting that the amount of lymph nodes harvested influences long-term survival, especially in carcinomas of the distal oesophagus. Nevertheless, there are definite concerns over decreased long-term HRQL in patients with extended lymph node dissections, especially related to phrenic and recurrent nerve palsy and the consequent risk of aspiration.

**Minimally invasive oesophagectomy**

The feasibility and safety of performing minimally invasive surgery, e.g. thoracoscopy and laparoscopy, for oesophageal cancer has been proven in experienced centres. According to a meta-analysis of published case series, this approach may lead to fewer anastomotic leaks and a faster postoperative recovery. Findings from a small single-centre study indicate that video-assisted thoracoscopic resection may result in less dyspnoea and better physical functioning than a transthoracic operation. However, significant selection bias
is present in all available studies and no prospective studies or randomised clinical trials have been performed.\textsuperscript{118}

\textbf{Early-stage cancer therapy}

A not insignificant proportion of the oesophageal cancers are superficial, early-stage tumours. In these tumours, lymphatic metastases are quite rare (less than 5\%),\textsuperscript{122} and they are being increasingly treated by less invasive techniques, mainly endoscopic mucosal resection and ablation.\textsuperscript{123} Limited surgery, e.g. vagal-sparing oesophagectomy, is an alternative in intramucosal cancers and might reduce morbidity without risk of recurrence, which may affect a fifth of the patients that undergo mucosal resection only.\textsuperscript{124}

\textbf{Oncological treatment}

The concept of adding preoperative radiation and chemotherapy to the surgical resection has been much disputed, but the discussion may have come to an end with a recent meta-analysis, showing an absolute 2-year survival benefit of 13\% for neoadjuvant chemoradiotherapy and 7\% for chemotherapy.\textsuperscript{125} Further follow-up confirmed an overall survival benefit at 5 years, but showed no statistically significant effect in squamous cell carcinoma patients in a subgroup analysis.\textsuperscript{126}

In randomised clinical trials, postoperative (adjuvant) oncological therapy has not been proven to confer a survival benefit in either type of oesophageal cancer,\textsuperscript{127-130} although adjuvant chemotherapy might prevent relapse in patients with squamous cell carcinoma.\textsuperscript{130}

A consistent finding in most studies that have evaluated neoadjuvant therapy is the achievement of a complete pathological response in a subset of patients, whereas the majority of patients may not benefit at all or not to any appreciable extent.\textsuperscript{131} This is a field of future research, where means of identifying responders would make further individualised therapy possible.\textsuperscript{132}

Finally, it has been proposed that definitive chemoradiotherapy may be as effective as surgery in the treatment of localised oesophageal cancer, especially for squamous cell carcinoma.\textsuperscript{133} Evidence is sparse, however, and local recurrences occur in the range of 16-54\% of cases,\textsuperscript{133} which may seem too high a price to pay, especially since salvage oesophagectomy, even in selected patients, entails even higher mortality and morbidity than the standard procedure.\textsuperscript{133,134}

\textbf{Palliative treatment}

Given that the large majority of patients do not qualify for surgery, mainly because of distant metastasis before diagnosis, there is a remarkable paucity in the literature concerning palliative management.\textsuperscript{135}
The aims of palliation in oesophageal cancer patients are to provide some local control, maintain HRQL and possibly prolong survival.\(^\text{136}\) For treatment of malignant dysphagia, there is currently no support for stricture dilatation, operative bypass procedures or supportive chemoradiotherapy owing to a high incidence of delayed complications and recurrent dysphagia. There is evidence, rather, favouring the use of self-expanding metal stents or intraluminal brachytherapy, of which the latter might provide a better HRQL and improved survival.\(^\text{135, 137}\)

**From mortality to morbidity**

As previously stated, some of the research focus has been shifted to attempts at reducing morbidity and improving the patients’ HRQL, especially since most oesophageal cancer patients, despite oesophagectomy, eventually die of their disease and in all likelihood suffer longstanding symptoms as a result of surgery.

**Perioperative morbidity**

*Surgical complications*

Owing to the varying definitions of surgical complications, it is difficult to appreciate the true incidence of such complications after oesophagectomy. Reported complication rates range from 10 to 27\% of cases.\(^\text{138-142}\) The wide range may be due to differences in definitions, in investigative measures, in patient selection, and in skill, and the latter might be a target for improvement. A most feared surgical complication, anastomotic leakage, still occurs relatively frequently, with figures reaching 5.5 to 9.0\% in population-based cohorts and large trials,\(^\text{95, 142, 143}\) but the previously reported increased fatality associated with anastomotic leaks has been disputed by reports from experienced centres.\(^\text{144-146}\) There is also conflicting evidence concerning the potential impact of surgical complications on long-term survival.\(^\text{138, 140, 141}\) One of the more obvious means of reducing complication frequencies would be to centralise surgery to more experienced hands, but the few population-based studies that have addressed high-volume surgery and the risk of surgical complications have so far provided conflicting results.\(^\text{95, 142, 149-151}\) Other complications of note are wound infections, chylothorax and recurrent nerve palsy.

*Medical complications*

Medical complications are even more common after oesophagectomy, mostly due to respiratory complications in the range of 17 to 41\%.\(^\text{95, 139, 142}\) The latter confer major risks to the postoperative oesophageal cancer patient and might be an independent predictor for in-hospital mortality.\(^\text{148}\) Cardiac arrhythmia and infarction are other common medical complications.
The health-related quality of life concept

A patient-reported outcome is defined as "any report coming directly from the study subject about a health condition and its treatment". Although there is no generally accepted definition of HRQL, most accept that it comprises patient-reported outcomes concerning several dimensions, including physical function, psychological function, social and role functions, and disease or treatment symptoms. To distinguish between the broader concept of quality of life and the more narrow concept of HRQL, the latter is reserved for aspects that are affected by disease or treatment for disease. Moreover, most investigators circumvent the absence of an agreed formal definition of HRQL by describing what they mean by the term HRQL and letting the items and scales in their questionnaire be intuitively understood.

Several models have been devised in attempts to characterise HRQL conceptually. One of the most frequently used was proposed by Wilson and Cleary, and outlines the relationships among measures of patient-reported outcomes. (Fig. 8) Importantly, this model highlights that HRQL is dependent on more than physical health alone, is modified by patient and environmental factors, and comprises symptoms, functional status and overall health perceptions.

Figure 8. Conceptual model of factors influencing health-related quality of life. Adapted from "Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes." 273(1):59-65. Copyright © 1995 American Medical Association. All rights reserved.

Finally, the model also emphasises the fact that HRQL is and must be a subjective measure. In contrast to a sign of disease, e.g. fever or high blood pressure (biophysiological variables, i.e. not a patient-reported outcome), a symptom is defined as "the subjective evidence of disease or physical disturbance", and thus can only be known about through a patient report. From a philosophical perspective, it might seem disturbing that subjectiveness is such an inherent quality of HRQL measures. There are, however, a number of theoretical and practical justifications for its status as a valid outcome, given the need for actually evaluating HRQL formally. First, there is no way of assessing symptoms and
functions without taking into account the patient report; second, even though the patient-reported outcome is ontically subjective, it is epistemically objective – that is, the symptoms do not exist outside of the patient, but they are interpreted identically by extraneous observers, for example as a number on an ordinal scale; third, a large body of evidence points to the fact that patient-reported outcomes in general and HRQL measures specifically are linked to hard end points such as development of cancer (e.g. self-assessed reflux disease is strongly associated with oesophageal adenocarcinoma) and mortality (e.g. HRQL measures are independent predictors of survival in oesophageal cancer patients), respectively.

**The rationale for the assessment of health-related quality of life**

HRQL is a relatively new outcome in medical research, but is increasingly used and it is nowadays considered standard practice to include HRQL in oncological clinical trials evaluating treatment effects. It has evolved as a separate outcome apart from mortality and morbidity, as it may answer the question of cost versus benefit when deliberating treatment alternatives. For instance, clinicians and patients would consider an oncological treatment with curative or palliative intent more or less worthwhile if they were aware of the effects on longevity as well as on symptom burden and well-being; the HRQL measures make the latter aspects formally evaluable. In the setting of oesophageal cancer in particular, HRQL measures may be more important than in most diseases in general, as the prognosis is very poor and most treatments have short- and long-term adverse effects. The inclusion of HRQL measures in surgical oncology has also been shown to influence clinical decision-making or to provide data as a basis for informed consent in a majority of randomised clinical trials, further strengthening the above reasoning.

**Measurement of health-related quality of life**

Questionnaires may be printed or terminal-based, and are filled in by the patient, or, less ideally, by a proxy; caregiver assessment of HRQL correlates poorly to the patient’s own view. The questionnaires used in the present research comprise both single-item scales and multi-item scales. In the former, the response to a single question is used to assess the aspect that is sought after, e.g. dyspnoea. Multi-item scales are used to measure less well defined symptoms, and especially functions, which may be conceptually complex, e.g. fatigue and emotional function, as different people may have different ideas as to their meaning.

Questionnaires need to take into account several key issues. These comprise validity, reliability, sensitivity, and responsiveness. Validity concerns whether or not the instrument is actually measuring the desired outcome, and may be evaluated by a combination of expert opinion, comparison with already known instruments,
and estimates of item correlation within scales as well as correlations between scales. Reliability concerns the random variability of the measurements, where the same patient suffering from the same symptoms would ideally report similar results at different times. Sensitivity relates to whether or not the instruments are able to detect differences between individual patients or groups of patients, and may be tested by considering different prognostic groups, for instance. Responsiveness is a related concept and signifies the ability to detect patient improvement or deterioration over time. However, as HRQL is indeed a subjective measure, one of the most important aspects, validity, can theoretically never be proven in any given instrument; it is only possible to corroborate the notion that the instrument itself is sensible and behaves as anticipated.

A plethora of well-constructed and extensively tested questionnaires of both general and disease-specific varieties are available. The former are designed to reflect states of health in people rather than patients, while the latter often focus on patient subgroups and their particular concerns and symptoms. One of the currently most used oncological questionnaires has been developed by the European Organisation for Research and Treatment of Cancer (EORTC), the EORTC Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), which is devised to measure cancer-general HRQL. In addition, there is an oesophageal cancer-specific module, the EORTC Quality of Life Questionnaire-Oesophageal 18 (EORTC QLQ-OES18), designed to be administered together with the core questionnaire.

Clinical relevance of health-related quality of life differences

Given a sufficiently large sample size, even minor HRQL differences may be detected and reach statistical significance. However, very small changes in HRQL may be imperceptible to the individual patient or may require treatment of a large number of patients to be worthwhile on the population level. It has therefore been generally recognised that not all HRQL effects are clinically pertinent.

In this thesis, the term clinical relevance is used. This is defined as the minimally clinically important difference, i.e. the smallest difference in score in the domain of interest that patients perceive as beneficial and that would cause clinicians to consider a change in the patient's management.

For determining such a minimally important difference, there are two main methods: the anchor-based and the distribution-based. In the former, comparisons are made with previously known measures that are more or less correlated with the HRQL outcomes, e.g. response to treatment, clinician-assessed performance status, disease severity, survival prediction. The other method is based on the statistical distribution of the results, including measures derived from the standard deviation of the mean scores. Current recommendations point out that patient-based and clinician-based anchors are the most appropriate to use in order to establish clinical relevance, along with clinical trial experience; only if
these are lacking may distribution-based methods be considered.\textsuperscript{166}

Two landmark studies concerning the EORTC QLQ-C30 questionnaire have formed the basis of the clinical relevance cut-off used in this thesis. First, King\textsuperscript{167} used data from 14 published studies and grouped patients according to multiple anchors such as performance status, weight loss, toxicity, and extent or severity of disease; mean score differences were compared within each group and the author concluded that a difference of 10 in mean scores may be interpreted as considerable symptom control, especially in the clinical trial setting. Second, Osoba \textit{et al}\textsuperscript{168} asked breast- and lung-cancer patients to fill in the core questionnaire at two time points, before and after chemotherapy; on the second occasion, the patients were also asked about perceived changes in physical, emotional and social functioning and in global quality of life. In that study, the group of patients with mean score changes from about 5 to 10 reported a 'little' change for better or worse; a 'moderate' change meant a change of about 10 to 20, while 'very much' change corresponded to a mean score change greater than 20.

The notion that a 10\% difference in a given scale is clinically relevant has gained considerable support, using within-person methods such as the one described above and other instruments concerning other disease states.\textsuperscript{154} Between-person approaches have, reassuringly, resulted in broadly similar estimates,\textsuperscript{169, 170} and would thus suggest that the use of a mean score difference of 10 or more as a measure of clinical relevance even between groups of patients is feasible. It must be pointed out, however, that there has been no investigation of the minimally clinically important difference in oesophageal cancer patients, subjected to surgery or otherwise, and moreover, there are no such data concerning the QLQ-OES18 instrument.

\textbf{Response shift}

The conceptual HRQL model (Fig. 8) incorporates a few levels usually unknown to the investigator and possibly to the patient. These are represented by environmental factors and innate characteristics. Possibly the former and certainly the latter form the basis for the concept of \textit{response shift}, where internal standards change over time and confer acceptance of disease, while symptoms are not perceived as detrimental as they would originally appear to be or even be.\textsuperscript{171} This aspect, although difficult to formally assess, may influence comparisons of HRQL outcomes over time.

\textbf{Health-related quality of life in oesophageal cancer patients}

Given the extent of the surgery performed for oesophageal cancer, it is no surprise that HRQL in this group of patients is particularly compromised.

\textit{Curative intent}

In a rare population-based study, Swedish patients operated on for oesophageal
cancer were assessed concerning HRQL 6 months after surgery. Compared with the general population, these patients reported reduced role and social function, while fatigue, appetite loss, diarrhoea, and dyspnoea were all prominent symptoms in the study group. Moreover, oesophageal-specific symptoms, such as cough, reflux, odynophagia, and dysphagia were also pronounced. Using the same data source and a follow-up measurement at 3 years, these HRQL impairments persisted to a large extent. Some single-institution studies with a longer follow-up confirm the deteriorated HRQL status in oesophagectomised patients: one showed a reduced physical function, prevalence of problematic dysphagia in 25% of patients, reflux symptoms in 60%, and postprandial dumping problems in half of the patients; in another it was claimed that half of the patients that had undergone transhiatal resection suffered from symptoms such as fatigue, dysphagia, and heartburn; a third, with an evaluation of survivors at 5 years, showed that most functioning measures were adequate compared to the general population, but that there were major persisting problems with reflux.

In one of the first longitudinal studies, physical and role functions were transiently reduced after oesophageal cancer surgery, but were restored within 6 to 9 months. These findings have been supported by subsequent studies, albeit small, and confirmed by follow-up of patients enrolled in a trial evaluating surgical approach in oesophageal tumours. In a recent study in which patients who survived after oesophagectomy were followed up for at least 3 years, these results were partly corroborated: the study group recovered most baseline HRQL measures after 6 to 9 months, but physical function, dyspnoea, diarrhoea and reflux were still worse at 3 years; emotional function, on the other hand, was improved.

As neoadjuvant therapy has been introduced as part of the therapeutic arsenal, some studies have addressed its impact on HRQL. From two relatively large studies it was concluded that multimodal therapy compared to surgery alone implied HRQL deterioration in the short-term, but that differences were negligible 6 months postoperatively.

Some, but not all, studies have shown that despite presence of symptoms and reduction in physical function, emotional function and global quality of life scores are either improved with time or better in comparison with the general population. This may be explained by the experience of response shift in these patients, but few studies have investigated this phenomenon. In the setting of major surgery for oesophageal or gastric cancer, some data indicate that response shift after surgery is responsible for re-evaluating the global quality of life scale; before surgery, it is determined by emotional and physical function, whereas 6 months postoperatively symptoms play a much greater role. Interestingly, it has also been suggested that response shift may be the reason why surgery after neoadjuvant therapy is associated with smaller HRQL reductions than after
surgery alone, as the first group of patients are already aware of potential symptoms when encountering postoperative problems.\textsuperscript{179}

\textit{Palliative intent}

Finally, the evaluation of HRQL is of paramount importance in palliative patients. Nevertheless, few studies have dealt with HRQL in this group. In a small study it was concluded that in patients who survived less than 2 years, oesophagectomy had a detrimental impact on HRQL, and these patients never regained baseline values, making it important to consider the indication for surgery thoroughly.\textsuperscript{12} In the context of a randomised controlled trial evaluating palliative therapies, it was also noted that all patients suffered large reductions in HRQL functions over time, whereas symptoms, especially dysphagia and deglutition problems, were alleviated by the intervention.\textsuperscript{182}

\textit{Biological mechanisms}

The conceptual model (Fig. 8) would require that changes in biophysiological variables take place to explain the patient-reported outcomes symptoms and subsequent function decrease. In patients operated on for oesophageal cancer, persistent dyspnoea may be explained by a reduced lung volume in the presence of an intrathoracic stomach, while postprandial dumping and diarrhoea would be related to surgical vagotomy. Reflux symptoms are most likely due to the excision of the lower oesophageal sphincter mechanism, thus distorting the anatomy and function.\textsuperscript{11, 18} Definitive support for these plausible mechanisms is lacking, however.

\section*{OESOPHAGEAL ADENOCARCINOMA SEX RATIO}

\subsection*{Enigmatic male predominance}

As already noted, the incidence rise in oesophageal adenocarcinoma has affected men to a greater extent than women,\textsuperscript{13} and the male to female sex ratio in worldwide registries has been estimated to be 7-10 to 1.\textsuperscript{17}

Currently, there is no generally accepted explanation for this high sex ratio, which is uncommon for a non-genital tumour.\textsuperscript{184} Theoretically, the difference may be a product of endogenous or exogenous exposure to known or unknown risk factors, or a combination of the two.

\subsection*{Difference in risk factor exposure}

Barrett’s oesophagus is, as discussed above, considered a step in the causal pathway to adenocarcinoma, and may be part of the puzzle. Further, the exposure to established risk factors such as reflux and obesity may be more common in men
than in women or act differently depending on gender.

**Sex distribution**

*Barrett’s oesophagus*

The risk of acquiring Barrett metaplasia is nearly doubled in men,\(^{185, 186}\) and the risk of adenocarcinoma development in those already afflicted is approximately halved in women.\(^{187}\) In a large referral-based endoscopy study, this difference in intestinal metaplasia was found to be age-dependent, where the prevalence was four times higher in young and middle-aged men than in women of similar age, who in turn seemed to develop the disease about 20 years later.\(^{188}\) These sex differences have hitherto not been explained, but may be related to differential risk factor impact and hormonal exposure differences (see below).

**Established risk factors**

The prevalence of reflux disease has not been shown to be higher in men,\(^{189, 190}\) whereas in Western societies overweight and obesity have been found to be more frequent in men.\(^{191, 192}\) Smoking is more prevalent in men, although this difference has begun to decrease in recent years.\(^{193, 194}\) Differences in NSAID use are harder to gauge, but aspirin use may be more common in women.\(^{195}\) Prevalence of infection with *H. pylori* seems to be at most slightly higher in men.\(^{196}\) To date, no study has evaluated all the above known risk factors in relation to the risk of male and female oesophageal adenocarcinoma, and it is therefore unclear whether sex differences in risk factor exposures alone might account for the male predominance.

**Differential risk factor impact**

*Male-type obesity*

As mentioned above, obesity seems to play a central role in the development of oesophageal adenocarcinoma. Not only a high BMI *per se*,\(^{16, 18, 34, 42}\) but also, and possibly more so, a large amount of intra-abdominal fat increases the risk of this cancer.\(^{42}\)

Few studies have dealt with the sex-specific impact of obesity. In a hospital-based study from Ireland, it was noted that obese men had four times as high a risk of incident adenocarcinoma as lean men, while no such association was found in women; these results were even more pronounced when the analyses were restricted to the distal oesophagus.\(^{197}\) These findings were supported by an Australian study, where a similar risk elevation was found in men only.\(^{34}\) Interestingly, the risk was even higher for obese individuals below 50 years of age, in whom female adenocarcinoma is almost non-existent. Moreover, in a study based on British primary care data a risk increase was found for overweight and obese men, while only obese women seemed to be at risk.\(^{18}\) However, some
conflicting evidence was produced from a population-based study in Sweden, where a high BMI was found to increase the risk substantially more for women than for men.\textsuperscript{198} These studies have in common a limited sample size concerning female cases, precluding any firm conclusions. Nevertheless, as obesity itself is slightly more common in men, visceral fat is definitely more prevalent in men, and some evidence indicates that abdominal obesity in general and a high male BMI may increase the risk of oesophageal adenocarcinoma, part of the sex ratio puzzle may have been solved.

\textit{Erosive and non-erosive reflux disease}

Reflux disease may or may not be accompanied by objective findings on endoscopy; when reflux causes local inflammation and ulceration in the oesophagus, it is termed erosive reflux disease. In a recent meta-analysis, erosive reflux disease was 57\% more common in men, while non-erosive reflux disease was 28\% less common, as compared to women.\textsuperscript{185} This may also contribute to the male predominance, as local inflammation is proposed as a step to intestinal metaplasia and subsequently cancer.\textsuperscript{28}

\textbf{The possible impact of sex hormones and reproductive factors}

There is now mounting evidence that the male predominance is dependent on age: the sex ratio at a younger age seems to be even larger, whereas the difference in incidence between older men and women may be smaller.\textsuperscript{19, 199, 200}

In line with other gastrointestinal tumours, it has been postulated that oestrogen may play a role in oesophageal adenocarcinogenesis, thus linking the above observation of age-dependency with menopausal changes in women. Some studies have confirmed the presence of oestrogen receptors in oesophageal tissue, and laboratory research conducted \textit{in vitro} suggests that oestrogen may have an inhibitory effect on carcinogenesis.\textsuperscript{184}

Epidemiological studies of endogenous as well as exogenous sex hormonal exposure have been conducted, mostly without revealing any associations. In population-based studies, no influence of childbearing could be discerned,\textsuperscript{201} and it was not that found that hormone replacement therapy affected adenocarcinoma incidence in women.\textsuperscript{202} Furthermore, oestrogen exposure in a national cohort of men with prostate cancer did not result in any decrease in the risk of oesophageal adenocarcinoma as a second cancer.\textsuperscript{203} However, an investigation of the effects of breastfeeding in a case-control study did indicate a dose-dependent risk reduction.\textsuperscript{204}

Some research has been conducted to evaluate the potential effects of tamoxifen, a selective oestrogen receptor modulator mostly acting as an anti-oestrogen, and used for breast cancer treatment. Early register data did not indicate an increased
risk for oesophageal adenocarcinoma as a second cancer in breast cancer patients after adjuvant tamoxifen therapy.\textsuperscript{205, 206} In a large population-based study, a 60% risk increase was noted, but it did not reach statistical significance.\textsuperscript{207}

Lastly, some researchers have advanced the hypothesis that androgen plays a role in adenocarcinogenesis.\textsuperscript{208} Androgen receptors have been identified in normal oesophageal tissue as well as in oesophageal adenocarcinoma tissue, with unclear significance.\textsuperscript{209, 210} In a prostate cancer cohort, the effects of anti-androgen therapy on the incidence of second oesophageal adenocarcinoma were evaluated, and a 30% statistically significant risk reduction was found.\textsuperscript{208} It is uncertain, however, whether this is an effect of anti-androgen treatment or whether prostate cancer itself is linked to aetiological factors that are inversely associated with oesophageal adenocarcinoma.

In conclusion, there is scant and conflicting evidence of hormonal influence on the risk of oesophageal adenocarcinoma, and the evidence is still not sufficient to explain the male predominance. On the other hand, there appears to be an accumulating amount of research indicating that established risk factors may act differentially on men and women: the male type of obesity and reflux disease might in fact be more dangerous regarding the risk of adenocarcinoma than their female counterparts.
Aims

The general aim of the studies summarised in this thesis was to advance the understanding about the morbidity after oesophageal cancer resection and the male predominance in oesophageal adenocarcinoma.

Specific aims were:

- To determine the association between selected surgical factors and HRQL 6 months after oesophagectomy for cancer.
- To establish the relation of hospital and surgeon volume to HRQL 6 months after oesophagectomy for cancer.
- To evaluate the influence of surgeon volume on the occurrence of technical surgical complications 30 days after oesophageal or cardia cancer resection.
- To clarify the age-dependency of the incidence rate ratio between incident male and female oesophageal and gastric cardia adenocarcinomas.
- To explore the sex distribution of established risk factors for oesophageal adenocarcinoma in the general population.
MATERIALS AND METHODS

In these studies data from nationwide epidemiological materials were used. Studies I, II and III were based on the Swedish Esophageal and Cardia Cancer (SECC) register, while study IV was based on the Swedish Cancer Register and study V used data from the Reference Population (RP) study, a national survey.

THE SWEDISH ESOPHAGEAL AND CARDIA CANCER REGISTER

Studies I, II and III were based on data from the SECC register, a nationwide database for research purposes in function from 2001 to 2005 inclusive. This register covered 97% of all institutions performing surgery and undertaking postoperative care with regard to oesophageal cancer patients.

Background and collection of data

The network forming the basis for the register was initially developed as a means of conducting a population-based study on risk factors for oesophageal and cardia cancer. Using the existing organisation, and adding adjustments to focus on oesophageal cancer surgery, the SECC register started to include patients on April 2, 2001. It was initiated in order to act as a resource for clinical research, aiming to improve the quality of the surgical treatment of the patients afflicted with oesophageal and cardia cancer in Sweden.

Out of 179 eligible hospital departments involved in the diagnosis and treatment of these cancer patients, representing general surgery, thoracic surgery, otorhinolaryngology, oncology and pathology, 174 (97%) participated in the register. At each site, there was an assigned contact physician, responsible for the local registration. The SECC register was co-ordinated by a central project administrator (Eja Fridsta), who received the histopathology report whenever an oesophageal cancer diagnosis was confirmed, and subsequently reminded the contact physician about the registration of the patient and the collection of data required. Informed consent was obtained from each living patient prior to inclusion in the register. Furthermore, the SECC register was also coordinated with all six Swedish regional cancer registries to ensure optimal completeness. The national participation rate among operated cases reached approximately 90%, where the non-participation was mainly due to physicians not asking patients for their consent.
Register information

The SECC register contains information on patient characteristics, tumour characteristics (histological type, specific site and stage), neoadjuvant therapy, surgical procedures, complications, length of hospital stay, HRQL data and survival.

Validity

The validity of the SECC register has not been formally evaluated. Several circumstances nevertheless point to a high intrinsic validity: the near perfect national coverage, the prospective data collection and the independent manual review of all case records. The data were thus not collected by the local contact physician or the operating surgeon, a potential source of bias. Further, quality was constantly ensured by the work of the project co-ordinator, who through repeated contacts with the responsible contact physicians ensured complete medical record retrieval for every patient.

HEALTH-RELATED QUALITY OF LIFE MEASUREMENTS

In studies I and II, EORTC questionnaires were used to measure HRQL. These are multidimensional in nature, and range from cancer-general and oesophageal-specific symptoms to physical and psychological functions and to even broader concepts such as global quality of life. In clinical studies incorporating these measures, it is important to include only aspects of HRQL that may plausibly and conceptually be affected by the intervention and adequately measurable, according to the study design.\textsuperscript{153} Hence, not all dimensions of the EORTC questionnaires were included in the current studies; excluded, for example, were financial problems and social function, as these aspects were deemed to be too distal to the disease process and the effects of the evaluated treatment and its determinants.

EORTC core questionnaire

The EORTC QLQ-C30 questionnaire is cancer-specific, structurally multidimensional and contains 30 items.\textsuperscript{164} It comprises five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea or vomiting), and a global quality of life scale. Furthermore, six single items are included that address problems or symptoms common among cancer patients in general, such as dyspnoea, appetite loss, insomnia, constipation or diarrhoea, and the perceived financial impact.

Every item has four categorical alternatives on an ordinal scale: 1) “Not at all”, 2)
"A little", 3) "Quite a bit", 4) "Very much", except for the global scale, where there are seven alternative responses, from 1) "Very poor" to 7) "Excellent". All items are to be assessed with the past week in mind.

The core questionnaire has been extensively tested for reliability, validity and responsiveness.\textsuperscript{164, 168, 211-213}

**EORTC oesophageal module**

The EORTC QLQ-OES18 is designed as a supplemental module to the core questionnaire in order to assess oesophageal-specific symptoms.\textsuperscript{165} There are four symptom scales (eating, reflux, oesophageal pain, and dysphagia) and six single items addressing cough, dry mouth, taste alteration, choking, speech and trouble swallowing saliva. This module uses the same response alternatives as the core questionnaire, within the same time frame.

Reliability and validity have been tested for QLQ-OES18, with excellent results for validity. Some intra-scale correlations were poor, e.g. reflux and oesophageal pain, but these scales were still retained for clinical purposes.\textsuperscript{165}

**Application of EORTC questionnaires**

The HRQL questionnaires employed in studies I and II have been extensively used in previous clinical research, in randomised clinical trials, and in observational studies.

**From items to scores**

Patient responses to the items posed in the EORTC questionnaires are termed raw scores and range from 1 to 4. HRQL scales ranging from 0 to 100 are subsequently constructed by combining raw scores, using a linear transformation procedure according to the EORTC scoring manual.\textsuperscript{214} Higher scores in the functional and the global quality of life scales represent a higher level of function and better global quality of life, respectively, whereas higher symptom scores constitute a greater degree and greater severity of symptoms.

Missing single items remained missing, whereas missing items in scales were imputed using the average values of the remainder of the existing scale items. If over half of the scale items were missing to begin with, no such imputation took place and those scales were defined as missing.\textsuperscript{214}

**Interpretation**

The exposure variables among technical surgical factors and surgical volume were evaluated regarding their impact on the HRQL outcomes, where the mean HRQL scores in the exposed group were compared between defined levels of exposure.
As discussed above, small changes in HRQL measures might not be appreciated either on the individual or on the group level, and based on previous research, mean score differences of 10 or more on the 0 to 100 scale denoted clinical relevance. Some research suggests that even lower figures may represent meaningful differences, but the higher cut-off was employed in order to prevent false-positive results.

**Time frame**

The HRQL assessment was performed 6 months after the oesophagectomy, and did not include a preoperative baseline assessment. Six months was chosen as previous research has shown that most acute symptoms after surgery have subsided after this time period, as reflected by a return to preoperative baseline values. Furthermore, at this point in time, tumour recurrence is an unlikely event and would therefore not materially influence HRQL measures.

**THE SWEDISH CANCER REGISTER**

**Background and collection of data**

Data from the nationwide Swedish Cancer Register were used in study IV. This register was established in 1958, when national cancer registration began in Sweden. Clinicians and pathologists are legally obliged to report all newly diagnosed cancers to regional cancer registers, which in turn report to the national register. The clinicians report both tumours that are biopsy-verified and those that are not, but for the majority of patients, the register receives double notification. Cancer diagnoses that are based on death certificates only are not registered, but the pathologist also reports incident cases discovered during autopsy. The diagnosis in the register is based on routine clinical examinations and is coded according to the International Classification of Diseases for Oncology (ICD-O). Notably, the register did not differentiate gastric cardia cancer from non-cardia gastric cancer until 1970.

**Validation**

Taking into account all cancer diagnoses, a recent validation study of the Swedish Cancer Register showed a slight non-random under-reporting, which increased with age and varied by site and histology. Regarding oesophageal and gastric cardia adenocarcinoma, the completeness is 98%, even though considerable misclassification within oesophago-gastric cancer sites has been shown. Nevertheless, the overall completeness of the Cancer Register is considered high and comparable to that of other high quality registers in northern Europe.
THE REFERENCE POPULATION STUDY

Background and collection of data

Study V was based on data from the RP study, a national survey of 6969 Swedish citizens conducted in 2008. The RP study was initiated as an effort to determine HRQL and frequency of gastrointestinal symptoms in the general population, as well as estimating the prevalence of risk factors for oesophago-gastric cancer in a sample likely to develop this type of cancer, as indicated by the relatively high age and male predominance of the participants.

The random sampling and data collection were carried out by Statistics Sweden (Statistiska Centralbyrån), using the highly complete and updated nationwide Swedish Total Population Register. The resulting sample corresponded to the age and sex distributions of oesophageal and gastric adenocarcinoma according to the new cases reported to the Swedish Cancer Register in the year 2006.

During the period April to July, inclusive, in the year 2008, 4910 (70.5% participation rate) individuals responded to the dispatched questionnaires.

Measurement of risk factors

Risk factor exposure was assessed by questions with categorical responses concerning symptoms and severity of reflux disease, tobacco smoking status, height and weight, formal education, frequency of NSAID use, and reflux treatment. Supplemental information for quality check and possible confounding included data on age and sex, also retrieved by means of every participant’s personal registration number, and data on physical activity.

Validation

The bulk of the questions regarding risk factor exposure in the RP study were derived from the questionnaires devised for a large British study conducted in the Bristol area in 1996 onwards. The validated questions from this study were translated to Swedish independently by several researchers in our group, after which a joint translation was produced by consensus. Subsequently, this translation was back-translated by a professional translator (Maud Marsden) and the result was compared with the original Bristol study questionnaire, in order to check for inconsistencies. Thereafter, the questionnaire was tested on some 20 individuals. Aided by these procedures, a final translation was created.
STUDIES I AND II

Design

Using the SECC register data from 2001 to 2005 inclusive, we performed two population-based cohort studies of the 355 patients who had undergone a macroscopically and microscopically radical oesophageal resection for cancer (R0 resection) and responded to the HRQL questionnaires EORTC QLQ-C30 and QLQ-OES18 6 months after surgery. Only patients with R0 resection were included, as any influence of surgical factors would have been negligible compared to the potential remaining tumour burden or recurrence, which has an impact on HRQL.\textsuperscript{176}

In study I, it was hypothesised that the following factors influence HRQL 6 months after oesophagectomy: 1) surgical approach, 2) type of resection, 3) lymph node dissection, 4) resection margin, 5) type of substitute, 6) perioperative bleeding, 7) duration of operation, and 8) surgical complications.

In study II, it was hypothesised that surgical volume affects HRQL 6 months after oesophageal resection, in terms of 1) hospital volume, 2) surgeon volume, and 3) individual high-volume institutions.

Statistical analyses

In study I, the evaluated exposure variables included surgical approach (transhiatal or transthoracic), type of resection (oesophagectomy, cardia resection, extended total gastrectomy, or total gastrectomy and oesophagectomy), extent of lymphadenectomy (<10, 10-20, or >20 examined lymph nodes), proximal resection margin (<10, 10-50, or >50 mm), oesophageal substitute (stomach, jejunum, or colon), type of anastomosis (handsewn, or stapled), perioperative blood loss (<500, 500-1000, or >1000 ml), duration of operation (<5, 5-9, or >9 h), and occurrence of early technical surgical complications (no or yes). The latter included postoperative bleeding exceeding 2000 ml or requiring a reoperation, anastomotic insufficiency, necrosis of the substitute, damage to the recurrent nerve, thoracic duct damage, or gastric perforation.

In study II, the impact of surgical volume was evaluated, and exposure variables included surgeon volume (<2, 2-6, or >6 annual operations) and hospital volume (<4, 5-9, or >9 annual operations). Hospital volume was categorised by accumulating operations performed on all patients, while surgeon volume was assessed as follows: all patients in the cohort were each assigned a primary, secondary, tertiary (if present), and quaternary surgeon (if present); every participating surgeon was considered to gain an increment of surgeon volume if that surgeon had ever been a primary surgeon in the cohort, and the patient was
assigned the surgeon volume of the involved surgeon with the highest cumulative surgeon volume. This method made sure that seniority took precedence, thus making the most experienced surgeon responsible for the surgical results. The cut-offs were predefined and based on previous research regarding surgeon volume, while a compromise was made between prior results and the need to provide sufficient hospitals in each category to allow comparative analyses, when considering hospital volume. As primary analyses failed to disclose any relevant outcome differences between strata regarding either hospitals or surgeons, the intermediate group in both cases was merged with the low-volume strata, thus producing only low- and high-volume surgery groups. Thus, low-volume surgeons (LVSs) and high-volume surgeons (HVSs) were defined as surgeons performing 6 or fewer, and more than 6 oesophageal resections for cancer annually, respectively; low-volume hospitals (LVHs) and high-volume hospitals (HVHs) were correspondingly defined as institutions conducting 9 or fewer, and more than 9 such operations per year, respectively.

The 6 month HRQL assessment was defined as the outcome in both study I and study II. Mean scores with 95% confidence intervals (CIs) were calculated; whenever mean score differences between different exposure groups were clinically relevant (≥10), a multivariable linear regression analysis was applied, using two models. Statistical significance was set at the 5% level. Missing data were handled according to the scoring manual.

A basic model included adjustments for age (<60, 60–70, or >70 years), sex, postoperative tumour stage (0–I, II, III or IV), number of predefined co-morbidities (0, 1-2, or ≥3), and number of predefined complications, occurring within 30 days after surgery (0, 1-2, or ≥3). Co-morbidity was categorised into five groups: 1) cardiopulmonary disorders, including hypertension, angina, heart insufficiency, emphysema or asthma; 2) diabetes; 3) hepatic or renal disease; 4) tobacco smoking; and 5) other significant disorders (such as other malignancies). Complications were grouped into technical surgical complications, defined as above; infections, including intra-abdominal or intrathoracic abscess, sepsis or wound infection; and respiratory complications (radiologically verified pneumonia, respiratory insufficiency requiring artificial ventilation or pulmonary embolus). Co-morbidities or complications within the same group were calculated only once. The basic model was chosen à priori to reflect patient characteristics and factors not evidently associated with the surgical technique.

In the full model, further adjustments were also made for histological tumour type (squamous cell carcinoma or adenocarcinoma), tumour location (upper and middle oesophagus, lower oesophagus, or cardia), surgical approach (transthoracic or transhiatal), neoadjuvant therapy (no or yes), and annual surgeon volume (<2, 2-6, or >6 operations), as appropriate. The extension to the basic model was also predefined and included factors more related to the surgery
itself. In study II, no adjustment was made for volume, as hospital and surgeon volume were strongly correlated, judged by the Spearman rank test (data not shown).

These models were applied in order to adjust for possible confounding between surgical factors and HRQL outcomes. Some covariates, such as age and sex, have been proven to affect HRQL measures and may also influence surgical decision-making. It is not difficult to fathom that factors such as tumour stage and co-morbidity, as well as extent of surgery, may have an impact on HRQL; furthermore, some covariates, e.g. tumour location and histology, might influence patient performance during and after surgery as squamous cell carcinoma is strongly associated to smoking, while adenocarcinoma is most often located distally and is associated with a different patient profile. Lastly, neoadjuvant therapy might make the patient more liable to suffer from complications, e.g. anastomotic breakdown due to fragile tissues.

STUDY III

Design

In study III, data from the 615 patients in the SECC register who underwent oesophageal resection from 2001 to 2005 inclusive were included in a population-based cohort study. It was hypothesised that surgeon volume influences the occurrence of early technical surgical complications.

Statistical analyses

The exposure, surgeon volume, was assessed in the same manner as in studies I and II. The category cut-offs were predefined and based on previous research. The outcome, i.e. technical surgical complications occurring within 30 days of surgery, was further divided into clinically pertinent subcategories: primary surgical complications, secondary surgical complications, and anastomotic leakage.

Primary surgical complications were those considered to be most closely linked to surgical skill and comprised major postoperative bleeding, anastomotic insufficiency, necrosis of the substitute, severe lymph leakage, gastric perforation, accidental splenectomy, and oesophago-tracheal fistula.

Secondary complications, in turn, were those considered somewhat less related to the individual surgeon, and included intra-abdominal abscess, empyema, wound infection, wound rupture, and bowel obstruction. Finally, anastomotic leakage was defined as anastomotic insufficiency, necrosis of the substitute, or oesophago-tracheal fistula. The occurrence of primary, secondary, and all technical
complications as well as anastomotic leakage was categorised into dichotomous outcomes (no or yes).

Frequency tables were constructed for descriptive purposes, stratified by surgeon volume categories as well as for individual high-volume surgeons.

Unconditional logistic regression was applied to derive odds ratios (ORs) and corresponding 95% CIs for the risk of surgical complications, using the high-volume surgeon group as reference. Adjustments for confounding were made in multivariable logistic regression models, each adjusted for clustering within individual surgeons. The latter correction was made since few surgeons belonged to the highest volume category, and this group may therefore have been artificially homogeneous as a result of other factors than volume alone. Three models were considered. First, a crude model, without adjustments, was applied. Second, a basic model was adjusted for age (<60, 60–70, or >70 years), sex, tumour stage (0–I, II, III, or IV), tumour location (cardia, lower oesophagus, or middle or upper oesophagus), histological type of tumour (squamous cell carcinoma or adenocarcinoma), and number of predefined co-morbidities (0, 1–2, or ≥3). Third, a full model included all variables in the basic model, and in addition surgical approach (transthoracic or transhiatal), extent of lymph node dissection (<10, 10–20, or >20 examined nodes), and neoadjuvant therapy (no or yes). Co-morbidity was defined as in studies I and II. The models above were predefined and conceived with reasoning similar to that in studies I and II. As in study II, the results could not be validly adjusted for hospital volume.

Fisher's exact test was used to evaluate the associations between individual high-volume surgeons and crude occurrence of surgical complications; the limited sample size in these stratified analyses did not allow valid adjustment for confounding.

**STUDY IV**

Study IV included several types of gastrointestinal adenocarcinoma. As only oesophageal and gastric cardia adenocarcinoma pertain to this thesis, the other cancer types are neither presented nor discussed.

**Design**

Study IV had a retrospective design and consisted of repeated cohorts with cross-sectional data from the Swedish Cancer Register during the period 1970 to 2006 inclusive. It was hypothesised that the incidence rate ratios between men and women for oesophageal and gastric cardia adenocarcinoma would be age-
dependent. Moreover, we set out to test the notion that the sex ratio would be stable before the female menopause, and decrease after menopause.

**Statistical analyses**

Study participants were identified by the following, predefined, criteria: (a) a first diagnosed cancer of oesophageal (ICD-7 150.0, 150.8 or 150.9) or gastric cardiac (ICD-7 151.1) origin, (b) the cancer was an adenocarcinoma (histology code 096) and (c) the cancer was the only cancer registered on the same date for that person (thus ensuring primary cancer identification). Information on cancer type, age at diagnosis and sex was retrieved for each patient from the Cancer Register, while Statistics Sweden provided demographic general population data, including the distributions of age and sex for each year.

The cancer cases were categorised into five-year age groups, beginning from 25 to 29 and ending with 80–84. For the different groups, annual incidence rates were calculated by dividing the number of incident cases each year by the annual male or female population, as appropriate. The male-to-female ratio of the incidence rates was subsequently derived for the corresponding age groups. Assuming a Poisson distribution, 95% CIs both for the incidence rate and for the male-to-female incidence rate ratio were calculated. These results were stratified into two time periods, 1970–1986 and 1987–2006, to examine period effects. These periods were chosen to incorporate the potential effect on tumour registration of introducing a revised diagnosis code system (ICD-9) in 1987. Because of the small number of young cases, the age groups below 40 years were merged when incidence rates and incidence rate ratios were calculated. As most previous research has considered age below 50 years, analyses were conducted and graphs constructed using this cut-off as well. Finally, the age-specific incidences of oesophageal and gastric cardia adenocarcinoma were modelled, using non-linear regression analysis.

**STUDY V**

**Design**

Study V was based on a population-based cross-sectional study using the RP study data base, comprising a randomly selected sample of 6969 Swedish citizens of ages 40 to 79, of whom 4906 (70.4%) were eligible and participated. The participants responded to questionnaires for assessment, among other issues, of their exposure to established risk factors for oesophageal adenocarcinoma.

We hypothesised that the evaluated risk factor distribution would differ between men and women in the following respects: 1) particular risk factor exposures, 2)
risk factor clusters, and 3) before and after the menopause.

**Statistical analyses**

**Study variables**

The questionnaire contained questions about the five study exposures, i.e. reflux disease, BMI, tobacco smoking, socio-economic status, and NSAID use, together with some general characteristics, including sex, age, and physical activity. Reflux disease was defined as heartburn or regurgitation occurring at least once a week during the last three months, or at least weekly use of antireflux medication during the same time period. Current BMI was calculated and categorised according to recommendations from the World Health Organisation (WHO). A BMI below 18.5 was considered to be underweight, a value of 18.5 to 24.9 was regarded as normal, 25 to 29.9 was defined as overweight, and 30 and above as obesity. Tobacco smoking status was defined as current, former, or never smoking. Participants who had ever smoked “one or more cigarettes a day for a year or more” and “smoked within the last 3 months” were classified as current smokers. Previous smokers were those who had ever smoked “one or more cigarettes a day for a year or more”, but had not smoked during the last 3 months. Never smokers had never smoked “one or more cigarettes a day for a year or more”. Socioeconomic status was proxied by length of formal education, which was categorised into <10 years, 10-12 years, or ≥12 years. NSAID use was defined as reported use of predefined and well-known brands of NSAIDs within the last 3 months. Four groups were devised, namely: no use of NSAIDs (or less than once a month), monthly use, weekly use, and daily use, in accordance with previous research. As aspirin is considered equivalent to NSAIDs concerning cancer preventive effects, it was treated as an NSAID and included in that variable.

**Regression models**

Prevalence rates of the study exposures were evaluated in men and women, using exposure frequencies and relative risk estimates. Unconditional multivariable logistic regression was used to calculate ORs with 95% CIs, and adjustment was made for confounding. Male sex was defined as outcome, reserving female sex as reference, while the aetiological factors constituted exposure. Two predefined multivariable models were applied. A basic model adjusted only for age (<60, 60-70, or >70 years), while the full model also adjusted for physical activity (several times a week, once a week, or less than once a week), reflux (no or yes), BMI (<25, 25-29.9, or ≥30), tobacco smoking status (never, previous, or current), education (≤9, 10-12, or >12 years), and NSAID use (ever or never). Physical activity was included as a potential confounder because of reported gender differences and a putative association with the exposures.

Furthermore, predefined exploratory analyses were conducted by combining
study variables, in which individuals with non-exposure were compared with exposed individuals regarding given combinations of the included variables. For example, individuals with BMI <25, without reflux who had never smoked, were compared with individuals with BMI ≥25, with reflux who had ever been smokers. Intermediate groups of exposure were included in the model, thus using all observations, but were not presented. Because of the expected small numbers in each category, these analyses were age-adjusted only.

Finally, a cut-off of 50 years was used to represent presumed menopausal effects. However, the statistical power proved to be inadequate, and the sample median (65 years) was instead employed for age-stratified analyses.
RESULTS

STUDIES I AND II

Some 609 patients treated with oesophageal resection were recorded in the SECC register during the study period. Of these, 163 (26.8%) died within 6 months after surgery or did not undergo a macroscopically and microscopically radical resection, and thus became ineligible for study. Registration was delayed in 67 (15.0%) of the 446 eligible patients and 24 (5.3%) patients did not wish to participate or did not respond, leaving 355 patients (79.6%) for analysis in studies I and II. Some clinical characteristics of these patients are presented in Table 2.

Table 2. Characteristics of participants in studies I and II.

<table>
<thead>
<tr>
<th></th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 60</td>
<td>91 (25.6)</td>
</tr>
<tr>
<td>60-70</td>
<td>127 (35.8)</td>
</tr>
<tr>
<td>&gt; 70</td>
<td>137 (38.6)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>287 (80.9)</td>
</tr>
<tr>
<td>Female</td>
<td>68 (19.2)</td>
</tr>
<tr>
<td><strong>Co-morbidity</strong></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>114 (32.1)</td>
</tr>
<tr>
<td>One or two</td>
<td>223 (62.8)</td>
</tr>
<tr>
<td>Three or more</td>
<td>17 (4.8)</td>
</tr>
<tr>
<td><strong>Tumour stage</strong></td>
<td></td>
</tr>
<tr>
<td>Stage 0-1</td>
<td>82 (23.1)</td>
</tr>
<tr>
<td>Stage II</td>
<td>120 (33.8)</td>
</tr>
<tr>
<td>Stage III</td>
<td>133 (37.5)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>18 (5.1)</td>
</tr>
<tr>
<td><strong>Tumour location</strong></td>
<td></td>
</tr>
<tr>
<td>Upper or middle oesophagus</td>
<td>53 (14.9)</td>
</tr>
<tr>
<td>Lower oesophagus</td>
<td>147 (41.4)</td>
</tr>
<tr>
<td>Cardia</td>
<td>155 (43.7)</td>
</tr>
<tr>
<td><strong>Tumour histology</strong></td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>84 (23.7)</td>
</tr>
<tr>
<td>Adenocarcinoma (or dysplasia)</td>
<td>271 (76.3)</td>
</tr>
<tr>
<td><strong>Neoadjuvant treatment</strong></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>318 (89.6)</td>
</tr>
<tr>
<td>Yes</td>
<td>37 (10.4)</td>
</tr>
<tr>
<td><strong>Hospital volume</strong></td>
<td></td>
</tr>
<tr>
<td>≤ 9 per year</td>
<td>174 (49.0)</td>
</tr>
<tr>
<td>&gt; 9 per year</td>
<td>181 (51.0)</td>
</tr>
<tr>
<td><strong>Surgeon volume</strong></td>
<td></td>
</tr>
<tr>
<td>≤ 6 per year</td>
<td>148 (41.7)</td>
</tr>
<tr>
<td>&gt; 6 per year</td>
<td>207 (58.3)</td>
</tr>
</tbody>
</table>
Demographic and tumour features among the non-eligible patients (mainly those who died before the 6-month follow-up) were similar to those of the study participants, except that the excluded patients had a more advanced tumour stage. In addition, the rate of technical surgical complications was nearly identical and no material differences were discerned regarding surgical volume (data not shown). Some questionnaire data were missing to a small degree: for individual items, the median proportion of missing data was 1% (range 0 to 4%), while total missing items comprised 1.1%.

**Surgical factors influencing health-related quality of life (study I)**

Some HRQL mean scores in relation to some surgical factors from study I are presented in Tables 3 and 4. Clinically relevant HRQL mean score differences from study I were analysed in linear regression models, where only the results from the full model are discussed, as both models behaved similarly.

**Surgical technique**

Patients undergoing transthoracic surgery and those in whom the resection was transhiatal reported similar functional levels of HRQL 6 months after surgery, although oesophagectomy with thoracotomy was associated with more dyspnoea and trouble with coughing. The latter effects were nevertheless attenuated after adjustment and did not reach statistical significance (data not shown). In a similar vein, the extent of lymphadenectomy did not have any clinically relevant impact on general symptoms or functions, or on oesophageal problems. However, mean score differences revealed that a proximal resection margin of less than 10 mm was followed by more problems with appetite loss and dysphagia: a statistically significant and clinically relevant effect on dysphagia remained in the adjusted analysis (mean score difference 14, 95% CI 1–28). Neither type of anastomosis seemed to be superior, as no clinically relevant mean score differences could be discerned. Finally, the small group that had undergone cardia resection seemed to suffer less from appetite loss, dysphagia and fatigue (data not shown). Other variables, including type of substitute, duration of operation, and perioperative blood loss were not associated with any clinically relevant differences between patient groups.

**Technical surgical complications**

The occurrence of technical surgical complications had detrimental effects regarding dyspnoea (mean score difference 9, 95% CI 0–18), fatigue (mean score difference 10, 95% CI 3–18), nausea or vomiting (mean score difference 9, 95% CI 3–16), coughing (mean score difference 17, 95% CI 8–25), physical function (mean score difference 9, 95% CI 4–15), global quality of life (mean score difference 10, 95% CI 4–16) and role function (mean score difference 13, 95% CI 4–22). These HRQL reductions persisted after adjustment.
Table 3. Surgical factors and health-related quality of life presented as mean scores with 95% confidence intervals (CIs) among 355 patients treated with oesophagectomy for cancer who responded to the EORTC QLQ-C30 questionnaire six months after surgery.

<table>
<thead>
<tr>
<th>Surgical approach</th>
<th>Number of patients (%)</th>
<th>Symptoms</th>
<th>Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Appetite loss</td>
<td>Dyspepsia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean score (95% CI)</td>
<td>Mean score (95% CI)</td>
</tr>
<tr>
<td>Transhiatal resection (reference)</td>
<td>56 (15.6)</td>
<td>39 (30-48)</td>
<td>23 (16.31)</td>
</tr>
<tr>
<td>Transhiatal resection</td>
<td>299 (84.2)</td>
<td>35 (31-39)</td>
<td>34 (31-38)</td>
</tr>
<tr>
<td>Examined lymph nodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 10 (reference)</td>
<td>116 (33.2)</td>
<td>36 (29-43)</td>
<td>30 (25.36)</td>
</tr>
<tr>
<td>10 - 20</td>
<td>142 (40.2)</td>
<td>37 (32-43)</td>
<td>36 (31-41)</td>
</tr>
<tr>
<td>&gt; 20</td>
<td>77 (21.7)</td>
<td>31 (23-39)</td>
<td>30 (23-37)</td>
</tr>
<tr>
<td>Proximal resection margin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 10 mm</td>
<td>17 (4.8)</td>
<td>48 (25-70)</td>
<td>41 (22-61)</td>
</tr>
<tr>
<td>10 - 50 mm (reference)</td>
<td>286 (74.9)</td>
<td>36 (32-40)</td>
<td>32 (29-36)</td>
</tr>
<tr>
<td>&gt; 50 mm</td>
<td>49 (13.3)</td>
<td>32 (22-42)</td>
<td>30 (20-40)</td>
</tr>
<tr>
<td>Type of anastomosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand-sewn (reference)</td>
<td>156 (43.9)</td>
<td>35 (30-41)</td>
<td>37 (31-42)</td>
</tr>
<tr>
<td>Stapled</td>
<td>193 (56.1)</td>
<td>36 (31-41)</td>
<td>39 (25-43)</td>
</tr>
<tr>
<td>Technical surgical complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (reference)</td>
<td>299 (84.2)</td>
<td>34 (31-38)</td>
<td>30 (27-34)</td>
</tr>
<tr>
<td>Yes</td>
<td>56 (15.6)</td>
<td>43 (33.53)</td>
<td>45 (36.54)**</td>
</tr>
</tbody>
</table>

† p value > .05.

* p value < .05

** p value < .001.
Table 4. Surgical factors and oesophagus-specific symptoms presented as mean scores with 55% confidence intervals (CIs) among 555 patients treated with oesophagectomy for cancer who responded to the EORTC QLQ-CES38 module six months after surgery (higher scores represent worse symptoms).

<table>
<thead>
<tr>
<th>Surgical approach</th>
<th>Number of patients (%)</th>
<th>Choking when swallowing</th>
<th>Trouble with coughing</th>
<th>Dysphagia</th>
<th>Trouble when eating</th>
<th>Reflux</th>
<th>Trouble swallowing saliva</th>
<th>Mean score (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transhiatal resection (reference)</td>
<td>56 (15.8)</td>
<td>12 (6-17)</td>
<td>13 (7-18)</td>
<td>29 (22-37)</td>
<td>37 (30-44)</td>
<td>25 (17-33)</td>
<td>17 (8-25)</td>
<td>25 (17-33)</td>
</tr>
<tr>
<td>Transhiatal resection</td>
<td>295 (84.2)</td>
<td>13 (18-24)</td>
<td>25 (25-32)**</td>
<td>22 (19-25)</td>
<td>34 (31-37)</td>
<td>25 (22-28)</td>
<td>13 (10-16)</td>
<td>25 (22-28)</td>
</tr>
<tr>
<td>Type of anastomosis</td>
<td>118 (33.2)</td>
<td>23 (18-27)</td>
<td>27 (22-32)</td>
<td>24 (20-28)</td>
<td>36 (32-40)</td>
<td>25 (20-25)</td>
<td>15 (11-20)</td>
<td>25 (20-25)</td>
</tr>
<tr>
<td>Hand-sewn (reference)</td>
<td>143 (40.3)</td>
<td>16 (13-20)</td>
<td>26 (21-30)</td>
<td>23 (19-27)</td>
<td>33 (30-37)</td>
<td>25 (21-29)</td>
<td>12 (8-15)</td>
<td>25 (21-29)</td>
</tr>
<tr>
<td>Proximal resection margin</td>
<td>77 (21.7)</td>
<td>12 (10-20)</td>
<td>16 (12-20)</td>
<td>40 (21-59)**</td>
<td>36 (23-48)</td>
<td>25 (14-37)</td>
<td>16 (8-23)</td>
<td>25 (14-37)</td>
</tr>
<tr>
<td>&lt; 10 mm</td>
<td>17 (4.8)</td>
<td>19 (16-22)</td>
<td>25 (21-30)</td>
<td>23 (20-26)</td>
<td>34 (31-37)</td>
<td>24 (21-27)</td>
<td>13 (10-15)</td>
<td>24 (21-27)</td>
</tr>
<tr>
<td>10 - 50 mm (reference)</td>
<td>266 (74.9)</td>
<td>21 (12-31)</td>
<td>34 (24-45)</td>
<td>39 (13-26)</td>
<td>35 (27-43)</td>
<td>28 (15-38)</td>
<td>16 (5-26)</td>
<td>28 (15-38)</td>
</tr>
<tr>
<td>Examinations of lymph nodes</td>
<td>10 (2.7)</td>
<td>13 (11-23)</td>
<td>26 (20-32)</td>
<td>25 (20-29)</td>
<td>33 (28-38)</td>
<td>24 (19-29)</td>
<td>13 (8-18)</td>
<td>24 (19-29)</td>
</tr>
<tr>
<td>&lt; 10 (reference)</td>
<td>116 (32.6)</td>
<td>24 (19-29)</td>
<td>27 (22-32)</td>
<td>24 (20-28)</td>
<td>32 (31-44)</td>
<td>28 (23-33)</td>
<td>15 (11-19)</td>
<td>28 (23-33)</td>
</tr>
<tr>
<td>&gt; 20</td>
<td>190 (51.6)</td>
<td>12 (8-17)</td>
<td>16 (19-33)</td>
<td>18 (13-24)</td>
<td>28 (24-33)</td>
<td>23 (17-28)</td>
<td>11 (6-16)</td>
<td>23 (17-28)</td>
</tr>
<tr>
<td>Surgical complications</td>
<td>296 (84.2)</td>
<td>14 (15-21)</td>
<td>23 (19-26)</td>
<td>22 (19-25)</td>
<td>33 (31-46)</td>
<td>25 (22-28)</td>
<td>13 (10-16)</td>
<td>25 (22-28)</td>
</tr>
<tr>
<td>Yes</td>
<td>56 (15.8)</td>
<td>24 (16-32)</td>
<td>43 (35.52)**</td>
<td>50 (22-38)</td>
<td>45 (31-48)</td>
<td>26 (18-34)</td>
<td>14 (8-21)</td>
<td>26 (18-34)</td>
</tr>
</tbody>
</table>

* p value < 0.05
** p value < 0.005
*** p value < 0.01
Influence of surgery volume on health-related quality of life (study II)

Since differences in the distributions of tumour location were found among the hospital and surgeon volume categories, stratified analyses of the oesophageal and cardia cancer locations were conducted.

Hospital volume

The symptom and functional scales 6 months after oesophageal cancer surgery were generally equal in LVHs and HVHs, and no mean score difference met the criteria for further analysis by linear regression. This also held true for HRQL mean score differences stratified for cancer location (data not shown).

Surgeon volume

Similarly, these HRQL scales were essentially equal among the LVSs and HVSs. The only difference in HRQL outcome that met the criterion for clinical relevance consisted of more trouble with coughing in the HVS group (a mean score difference of 12), which was slightly attenuated after adjustment but remained statistically significant (mean score difference 9, 95% CI 2–15). Stratified analyses revealed no clinically relevant mean score differences in the cardia location, but worse trouble with coughing remained clinically relevant and was statistically significant in the HVS group (mean score difference 12, 95% CI 2–21).

Hospital differences

Comparisons of the mean scores of the four HVHs included in the study showed only minor differences. Appetite loss, diarrhoea, and oesophageal-related pain did differ between the separate HVHs to a clinically relevant extent, but no trend of any association between higher hospital volume and better HRQL scores was discerned (data not shown).
STUDY III

As the entire SECC register from 2001 to 2005 inclusive was used, study III included 615 patients. Clinical characteristics stratified by surgeon volume categories are presented in Table 5.

Table 5. Clinical characteristics of the participants in study III.

<table>
<thead>
<tr>
<th>Surgeon volume*</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High n=347</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>&lt; 60</td>
<td>87 (25.1)</td>
</tr>
<tr>
<td>60-70</td>
<td>117 (33.7)</td>
</tr>
<tr>
<td>&gt; 70</td>
<td>143 (41.2)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>279 (80.4)</td>
</tr>
<tr>
<td>Female</td>
<td>68 (19.6)</td>
</tr>
<tr>
<td>Co-morbidity</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>108 (31.1)</td>
</tr>
<tr>
<td>One or two</td>
<td>223 (64.3)</td>
</tr>
<tr>
<td>Three or more</td>
<td>16 (4.6)</td>
</tr>
<tr>
<td>Tumour stage</td>
<td></td>
</tr>
<tr>
<td>Stage 0-I</td>
<td>72 (20.7)</td>
</tr>
<tr>
<td>Stage II</td>
<td>97 (28.0)</td>
</tr>
<tr>
<td>Stage III</td>
<td>139 (40.1)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>38 (11.0)</td>
</tr>
<tr>
<td>Tumour location</td>
<td></td>
</tr>
<tr>
<td>Cardia</td>
<td>140 (40.3)</td>
</tr>
<tr>
<td>Lower oesophagus</td>
<td>139 (40.1)</td>
</tr>
<tr>
<td>Upper or middle</td>
<td>68 (19.6)</td>
</tr>
<tr>
<td>Tumour histology</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>104 (30.0)</td>
</tr>
<tr>
<td>Adenocarcinoma (or dysplasia)</td>
<td>243 (70.0)</td>
</tr>
<tr>
<td>Neoadjuvant treatment</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>314 (90.5)</td>
</tr>
<tr>
<td>Yes</td>
<td>33 (9.5)</td>
</tr>
<tr>
<td>Macroscopically radical</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>314 (90.5)</td>
</tr>
<tr>
<td>No</td>
<td>33 (9.5)</td>
</tr>
</tbody>
</table>

* High, medium and low surgeon volumes are defined as more than 6, 2 to 6, and below 2 oesophagectomies per year, respectively.

Age, sex, co-morbidity and tumour stage were similarly distributed among the surgeon volume categories, while some slight differences were noted regarding tumour location and histology, where HVSs seemed to manage more proximal
tumours of the squamous cell carcinoma type. Regarding neoadjuvant treatment and achievement of macroscopical radicality, no major differences were seen (Table 5). The frequencies of technical surgical complications are presented in Figure 9.

Major complications of a non-technical nature were recorded in 217 patients (35.3%) and the postoperative mortality within 30 days of surgery amounted to 17 patients (2.8%). Technical complications by surgeon volume categories are presented in Figure 9. Any such complication afflicted 154 patients (25.0%), whereas anastomotic leakage was detected in 56 patients (9.1%) postoperatively.

![Surgical complications](image)

**Figure 9.** Technical surgical complications among the 615 studied patients, stratified by high-volume surgeons (HVSs), medium-volume surgeons (MVSs), and low-volume surgeons (LVSs).

**Surgeon volume and technical complications**

Even though adjustment was made for confounding, the risk of technical surgical complications was not lower in the HVS group than in the MVS and LVS groups (Table 6). The adjusted point estimates for primary complications rather suggested a lower risk among LVSs (OR 0.49, 95% CI 0.19–1.42) and MVSs (OR 0.66, 95% CI 0.38–1.17), than in the HVS group, but these differences were not statistically significant. Furthermore, the results for secondary complications indicated that the risk was higher in the LVS (OR 1.41, 95% CI 0.65–3.08) than in the HVS group. But again, this apparent disparity was not statistically significant.
Individual high-volume surgeons

Eight surgeons in study III performed more than 6 oesophageal resections per year during the study period, and were thus defined as HVSs. Unadjusted comparisons, using Fisher’s exact test and with the surgeon with the highest annual volume as reference, revealed no apparent trend of more complications with a lower case load among these individual surgeons (data not shown). Compared with the surgeon performing the largest number of resections, the second most frequent operator displayed significantly fewer primary and secondary complications combined (p value < 0.042). Moreover, the sixth most frequently operating surgeon had more secondary complications (p value < 0.001), whereas the seventh most frequent operator had significantly more anastomotic leaks (p value < 0.011).
Table 6. Risk of surgical complications after oesophagectomy for cancer among the 615 studied patients, expressed as odds ratios (ORs) with 95% confidence intervals (CIs), by surgeon volume category.

<table>
<thead>
<tr>
<th>Surgical complications</th>
<th>Patients (%) n=615</th>
<th>High-volume surgeons</th>
<th>Medium-volume surgeons</th>
<th>Low-volume surgeons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients (%) n=547</td>
<td>Grade OR (95% CI)</td>
<td>Patients (%) n=199</td>
<td>Grade OR (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Basic OR (95% CI)*</td>
<td></td>
<td>Basic OR (95% CI)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Full OR (95% CI)*</td>
<td></td>
<td>Full OR (95% CI)*</td>
</tr>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>1.04 (16.0)</td>
<td>0.67 (0.41-1.10)</td>
<td>39 (14.1)</td>
<td>0.54 (0.22-1.32)</td>
</tr>
<tr>
<td>Major</td>
<td>68 (10.6)</td>
<td>0.70 (0.41-1.22)</td>
<td></td>
<td>0.36 (0.18-0.71)</td>
</tr>
<tr>
<td>Major</td>
<td>0.66 (0.39-1.17)</td>
<td></td>
<td></td>
<td>0.49 (0.19-1.24)</td>
</tr>
<tr>
<td>Secondary</td>
<td>92 (15.1)</td>
<td>0.75 (0.36-1.66)</td>
<td>21 (10.6)</td>
<td>1.62 (0.82-3.23)</td>
</tr>
<tr>
<td>Major</td>
<td>47 (13.5)</td>
<td>0.61 (0.32-1.16)</td>
<td></td>
<td>1.59 (0.76-3.32)</td>
</tr>
<tr>
<td>Major</td>
<td>0.83 (0.42-1.65)</td>
<td></td>
<td></td>
<td>1.41 (0.65-3.08)</td>
</tr>
<tr>
<td>Primary or secondary</td>
<td>154 (25.0)</td>
<td>0.76 (0.49-1.28)</td>
<td>43 (21.6)</td>
<td>1.05 (0.52-2.03)</td>
</tr>
<tr>
<td>Major</td>
<td>92 (26.5)</td>
<td>0.61 (0.46-1.40)</td>
<td></td>
<td>2.16 (0.59-2.29)</td>
</tr>
<tr>
<td>Major</td>
<td>0.60 (0.45-1.42)</td>
<td></td>
<td></td>
<td>0.99 (0.49-1.98)</td>
</tr>
<tr>
<td>Anatomic leakage†</td>
<td>56 (9.1)</td>
<td>0.98 (0.52-1.86)</td>
<td>18 (5.0)</td>
<td>0.94 (0.37-2.36)</td>
</tr>
<tr>
<td>Major</td>
<td>32 (5.2)</td>
<td>1.00 (0.52-1.94)</td>
<td></td>
<td>0.74 (0.28-1.95)</td>
</tr>
<tr>
<td>Major</td>
<td>0.96 (0.49-1.92)</td>
<td></td>
<td></td>
<td>0.63 (0.22-1.82)</td>
</tr>
</tbody>
</table>

* The basic model included adjustments for age, sex, tumour stage, tumour location, tumour histology, and comorbidity.
† The full model included adjustments for age, sex, tumour stage, tumour location, tumour histology, comorbidity, surgical approach, neoadjuvant therapy, macroscopic radicality, and examined lymph nodes.
‡ Major postoperative bleeding, anastomotic insufficiency, necrosis of the substitute, severe lymph leakage, gastric perforation, accidental splenectomy, or oesophago-tracheal fistula.
§ Upper abdominal abscess, empyema, wound infection, wound rupture, or bowel obstruction.
# Anastomotic insufficiency, necrosis of the substitute, or oesophago-tracheal fistula.
STUDY IV

Some 147,919 patients aged 25 to 84 years with a primary gastrointestinal adenocarcinoma were identified during the study period 1970 to 2006 inclusive. Of these, 2544 had an oesophageal adenocarcinoma, whereas 4692 were afflicted by gastric cardia adenocarcinoma. In patients with oesophageal adenocarcinoma, the male and female mean ages at onset were 67.1 and 71.6 years, respectively; in those with gastric cardia adenocarcinoma, the corresponding mean ages were 67.5 and 69.2 years. The crude male and female incidence rates for adenocarcinoma of the oesophagus were 2.0 and 0.4 per 100,000 person-years, respectively, while the corresponding figures for the gastric cardia were 3.7 and 1.0.

Sex ratio

The overall male:female ratio for the incidence rate of adenocarcinoma of the oesophagus was 5.1:1, and that of the cardia, 3.7:1. The age-specific sex ratios are displayed in Figure 10.

**Figure 10.** Sex ratios stratified by age groups for oesophageal and gastric cardia adenocarcinoma in Sweden from 1970 to 2006 inclusive.

The sex ratio for oesophageal adenocarcinoma in younger age groups approached 10:1, while this ratio declined to below 4:1 in the oldest patients. There was a more constant sex ratio with age of about 4:1 concerning gastric cardia adenocarcinoma, although this also declined in the oldest age groups (Fig. 10). Owing to the relatively small number of female cases of oesophageal adenocarcinoma, the corresponding 95% CIs were wide in the younger strata (data not shown).
Sex-specific incidence and curve modelling

Crude incidence rates and modelled curves for both male and female oesophageal and gastric cardia adenocarcinoma are presented in Figure 11.

Figure 11. Modelling of age-specific incidence rates (per 100,000 person-years) by sex for oesophageal and gastric cardia adenocarcinoma from 1970 to 2006 inclusive.

For both oesophageal and gastric cardia adenocarcinoma, the male incidence rose steadily with age, up to the age-group 70–74 years, after which the incidence rate seemed to level out. The corresponding female incidence slope showed a delayed rise until the age of 70–74 years; this rise stabilised in the subsequent age groups, never reaching the same steep slope as the male counterpart. The modelling of the incidence curves using non-linear regression analysis confirmed the impression of
different slopes for men and women and of an increasing delay in the female incidence rise for oesophageal and cardia adenocarcinoma.

**Period effect**

Sex ratios for oesophageal and gastric cardia adenocarcinoma were calculated in 1970-1986 and 1987-2006, and comparisons between these periods revealed essentially similar patterns (data not shown).

**STUDY V**

Among the 4906 Swedish citizens who were eligible for and participated in this cross-sectional study, 3,220 (65.6%) were men and 1,686 (34.4%) were women, with participation rates of 69.5% and 72.6%, respectively. Non-participation was more common in younger age groups; 53.0% of those invited at ages 40-44 years responded, whereas 75.2% of those aged 75-79 replied. The mean ages of the male and female participants were 65.2 (standard deviation (SD) 9.4) and 63.9 (SD 10.7) years, respectively. The level of physical activity did not differ between men and women (data not shown).

**Distribution of separate risk factors in men and women**

Prevalence frequencies and logistic regression results are presented in Table 7. As the results from the basic and the full model were similar, only those for the latter are presented.

It is notable that reflux was less common in men than in women, and adjusted analyses revealed a statistically significant difference (OR 0.70, 95% CI 0.58–0.84). In contrast adjusted analyses revealed an almost twofold increase in the odds of being overweight in men, as compared to women (OR 1.98, 95% CI 1.72–2.21); this sex difference was less marked for obesity, but still prevailed (OR 1.22, 95% CI 1.01–1.47). Former tobacco smokers were more prevalent among men than in women, as compared to never smokers (OR 1.50, 95% CI 1.30–1.72), while no statistically significant difference was found for current smoking (data not shown). Apart from the finding that the intermediate education level (9 to 12 years) was more common in men, no essential gender differences were shown regarding years of education (data not shown). Finally, no use of NSAID proved to be more prevalent in men, with daily use as reference (OR 1.35, 95% CI 1.14–1.59).
Evaluation of clustering

When the effect of simultaneous exposure to all studied variables was assessed, a marked male predominance became evident whenever the NSAID exposure was included; for example when all five factors were evaluated, an almost threefold increase in the odds of being male with the aforementioned risk factors was detected (OR 2.76, 95% CI 1.21–6.32). However, these differences disappeared in all risk factor combinations where the NSAID variable was excluded (data not shown).

Table 7. Sex-specific prevalence rates and results of logistic regression analyses with odds ratios (ORs) and 95% confidence intervals (CIs) in a randomly selected sample of 4,906 Swedish citizens, using risk factors as exposures and male sex as outcome.

<table>
<thead>
<tr>
<th>Selected risk factors</th>
<th>Men</th>
<th>Women</th>
<th>Full model b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 3,220 (65.6%)</td>
<td>N = 1,686 (34.4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Reflux c</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2,711 (84.2)</td>
<td>1,301 (77.2)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Yes</td>
<td>330 (10.2)</td>
<td>227 (13.5)</td>
<td>0.70 (0.58-0.84)</td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 (normal weight)</td>
<td>1,120 (34.8)</td>
<td>790 (46.9)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>25-30 (overweight)</td>
<td>1508 (46.8)</td>
<td>538 (31.9)</td>
<td>1.98 (1.72-2.27)</td>
</tr>
<tr>
<td>≥30 (obese)</td>
<td>435 (13.5)</td>
<td>254 (15.1)</td>
<td>1.22 (1.01-1.47)</td>
</tr>
<tr>
<td>Missing</td>
<td>157 (4.9)</td>
<td>104 (6.2)</td>
<td></td>
</tr>
<tr>
<td>Tobacco smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1,459 (45.3)</td>
<td>890 (52.8)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>1,210 (37.6)</td>
<td>480 (28.5)</td>
<td>1.50 (1.30-1.72)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>445 (13.8)</td>
<td>233 (13.8)</td>
<td>1.18 (0.98-1.42)</td>
</tr>
<tr>
<td>Formal education (proxy for SES)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;12 years</td>
<td>771 (23.9)</td>
<td>475 (28.2)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>9-12 years</td>
<td>397 (12.3)</td>
<td>119 (7.1)</td>
<td>2.10 (1.65-2.68)</td>
</tr>
<tr>
<td>≤9 years</td>
<td>1,953 (60.7)</td>
<td>1,034 (61.3)</td>
<td>1.07 (0.92-1.24)</td>
</tr>
<tr>
<td>NSAID use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>608 (18.9)</td>
<td>356 (21.1)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Weekly</td>
<td>216 (6.7)</td>
<td>170 (10.1)</td>
<td>0.83 (0.64-1.06)</td>
</tr>
<tr>
<td>Monthly</td>
<td>217 (6.7)</td>
<td>156 (9.3)</td>
<td>0.89 (0.68-1.15)</td>
</tr>
<tr>
<td>No use d</td>
<td>2023 (62.8)</td>
<td>926 (54.9)</td>
<td>1.35 (1.14-1.59)</td>
</tr>
</tbody>
</table>

Abbreviations: SES = socioeconomic status; NSAID = non-steroidal anti-inflammatory drug.

a Adjusted for age.
b Adjusted for age, physical activity, reflux, education, body mass index, smoking status, NSAID use.
c Defined as at least weekly symptoms of acid regurgitation and/or heartburn and/or weekly use of gastro-oesophageal reflux disease treatment such as proton pump inhibitors, antacids, or H2-blockers.
d No use or less than once a month.
Age effect

Stratifying for age by using the sample median of 65 years produced the prevalence figures and logistic regression results shown in Table 8. When point estimates for ages below and above the aforementioned cut-off were compared, these exploratory analyses indicated that overweight (OR 2.41, 95% CI 1.99-2.93 versus OR 1.63, 95% CI 1.33-1.99) and obesity (OR 1.74, 95% CI 1.33-2.29 versus OR 0.87, 95% CI 0.67-1.13) were more associated with male sex than female sex at younger ages, as compared to older ages. Previous (OR 1.04, 95% CI 0.86-1.27 versus OR 2.18, 95% CI 1.79-2.67) and current (OR 0.97, 95% CI 0.76-1.24 versus OR 1.41, 95% CI 1.05-1.90) smoking was less strongly linked to men at younger ages than to men at older ages. Younger men had a shorter education than younger women (≤9 years: OR 1.38, 95% CI 1.13-1.67), while this association was reversed at older ages (≤9 years: OR 0.77, 95% CI 0.61-0.98). Finally, no use of NSAID seemed to be similarly more frequent in younger and older men, as compared to women (OR 1.26, 95% CI 0.95–1.67 versus OR 1.31, 95% CI 1.07–1.61) (Table 8).
Table 8. Age-stratified analyses with odds ratios (ORs) and 95% confidence intervals (CIs), using male sex as outcome.

<table>
<thead>
<tr>
<th>Selected risk factors</th>
<th>Men ≤65 (N = 1,579, 65.3%)</th>
<th>Age ≤65 Women (N = 805, 65.3%)</th>
<th>Full model.a</th>
<th>Men &gt;65 (N = 1,701, 67.4%)</th>
<th>Age &gt;65 Women (N = 867, 62.0%)</th>
<th>Full model.a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>OR (95% CI)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td><strong>Reflux</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1119 (86.8)</td>
<td>716 (82.8)</td>
<td>1.00 (reference)</td>
<td>1392 (81.8)</td>
<td>585 (71.3)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Yes</td>
<td>147 (9.7)</td>
<td>112 (12.9)</td>
<td>0.70 (0.53-0.92)</td>
<td>103 (10.8)</td>
<td>115 (14.0)</td>
<td>0.69 (0.53-0.90)</td>
</tr>
<tr>
<td><strong>Body Mass Index</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 (normal weight)</td>
<td>513 (33.8)</td>
<td>453 (52.4)</td>
<td>1.00 (reference)</td>
<td>607 (35.7)</td>
<td>337 (41.0)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>25-30 (overweight)</td>
<td>734 (48.3)</td>
<td>269 (31.1)</td>
<td>2.41 (1.99-2.93)</td>
<td>774 (45.5)</td>
<td>249 (29.5)</td>
<td>1.63 (1.33-1.99)</td>
</tr>
<tr>
<td>≥30 (obese)</td>
<td>219 (14.4)</td>
<td>110 (12.7)</td>
<td>1.74 (1.33-2.25)</td>
<td>216 (12.7)</td>
<td>144 (17.5)</td>
<td>0.87 (0.67-1.13)</td>
</tr>
<tr>
<td><strong>Tobacco smoking status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>700 (46.1)</td>
<td>405 (46.8)</td>
<td>1.00 (reference)</td>
<td>759 (44.6)</td>
<td>485 (50.1)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>522 (34.4)</td>
<td>281 (32.5)</td>
<td>1.04 (0.86-1.27)</td>
<td>608 (36.4)</td>
<td>199 (23.2)</td>
<td>2.18 (1.70-2.87)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>265 (17.4)</td>
<td>154 (17.8)</td>
<td>0.97 (0.75-1.24)</td>
<td>180 (10.5)</td>
<td>70 (8.6)</td>
<td>1.41 (1.05-1.90)</td>
</tr>
<tr>
<td><strong>Formal education (SES)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;12 years</td>
<td>460 (30.3)</td>
<td>355 (41.2)</td>
<td>1.00 (reference)</td>
<td>311 (18.3)</td>
<td>115 (14.5)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>9-12 years</td>
<td>249 (16.4)</td>
<td>80 (9.3)</td>
<td>2.10 (1.53-2.60)</td>
<td>146 (8.6)</td>
<td>30 (3.7)</td>
<td>2.14 (1.35-3.37)</td>
</tr>
<tr>
<td>≤9 years</td>
<td>771 (50.8)</td>
<td>399 (46.1)</td>
<td>1.38 (1.13-1.67)</td>
<td>1182 (63.5)</td>
<td>635 (77.3)</td>
<td>0.77 (0.61-0.98)</td>
</tr>
<tr>
<td><strong>NSAID use</strong>&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>608 (18.9)</td>
<td>359 (21.1)</td>
<td>1.00 (reference)</td>
<td>441 (25.9)</td>
<td>256 (31.2)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Weekly</td>
<td>216 (6.7)</td>
<td>173 (10.1)</td>
<td>0.71 (0.49-1.05)</td>
<td>110 (6.5)</td>
<td>76 (9.3)</td>
<td>0.85 (0.64-1.12)</td>
</tr>
<tr>
<td>Monthly</td>
<td>217 (6.7)</td>
<td>156 (9.3)</td>
<td>0.71 (0.49-1.02)</td>
<td>79 (4.6)</td>
<td>57 (6.7)</td>
<td>1.15 (0.74-1.78)</td>
</tr>
<tr>
<td>No use</td>
<td>2221 (68.8)</td>
<td>926 (54.4)</td>
<td>1.26 (0.95-1.67)</td>
<td>646 (55.6)</td>
<td>368 (43.2)</td>
<td>1.35 (1.07-1.62)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Adjusted for physical activity, reflux, education, body mass index, smoking status, NSAID use

<sup>b</sup> Defined as at least weekly symptoms of acid regurgitation and/or heartburn and/or weekly use of gastro-oesophageal reflux disease treatment such as proton pump inhibitors, antacids, or H2 blockers

<sup>c</sup> No use or less than once a month
DISCUSSION

METHODOLOGICAL CONSIDERATIONS

In the research described in this thesis epidemiological methods have been used to identify risk factors for morbidity and HRQL related to oesophageal cancer surgery, as well as to evaluate differences between men and women concerning the incidence of oesophageal adenocarcinoma and the corresponding risk factor exposure. The term epidemiology was formerly used to denote the study of occurrence of illness, but has evolved to the modern concept of "the distribution and determinants of disease in human populations."²²³

There are two main types of epidemiological studies: experimental and observational. There is a general perception in today's evidence-based medicine that experimental studies, and more to the point, randomised control trials in humans, yield the most reliable results regarding disease causation and treatment effects. Critics of the current evidence hierarchy point out that there is no inherent superiority in the means of achieving a result, as long as the result itself is valid. Thus, it is claimed that randomisation is but a way of reducing confounding, whereas more important aspects such as allocation concealment (blinding), completeness of follow-up, similarity of outcome measures and clinical characteristics are downplayed. The latter aspects could be applied in any trial, randomised or not, where stringent inclusion and exclusion criteria may also be utilised.²²⁴, ²²⁵ In this sense, the hierarchy of evidence might instead be interpreted as a hierarchy of comparative internal validity, where randomisation is but a means to ensure less bias; given that all other sources of bias are equal, the randomised clinical trial may exhibit higher internal validity.²²⁶ This reasoning has also found support in the literature, where meta-analyses of results derived from well-designed observational cohort and randomised interventional studies have shown that treatment effects in various fields are virtually identical.²²⁷

The above discussion is especially pertinent to studies I-III, where the several surgical factors and surgery volume hardly could have been randomised to the participants, as it would have been ethically unfeasible and also highly impractical, given the costs of several randomised controlled trials. It may also be noted that, given the low overall incidence and resection rate of oesophageal cancer, any such trial, examining for example one surgical factor, would have been severely underpowered.
Study design

Two types of observational studies have been used in this research: cohort studies and cross-sectional studies (explained below). In theory, most study designs may also be either prospective or retrospective. Several definitions of these abound, but these terms most commonly refer to the timing of the exposure assessment in relation to the outcome; the study is termed prospective if the exposure data are measured before the outcome has occurred, and retrospective if not. The point in labelling studies as such would be to indicate the possibility that the outcome may influence the exposure ascertainment; however, these concerns might also be entirely eliminated in retrospective studies, if methods are used to preclude this possibility. For example, studies IV and V are termed retrospective, as the outcomes (cancer and sex, respectively) are known and measured before the exposures are ascertained (age and sex, and risk factors, respectively). Nonetheless, there is hardly a fathomable way that this information could have influenced the outcome assessment, as age and sex are not particularly prone to misclassification, either systematic or random. Studies I-III may safely be termed prospective, as the exposure data were assessed before the outcome in each study.

Cohort studies

In the traditional cohort study examining the occurrence of a given disease, two groups are defined that are initially free of the disease and that differ regarding exposure to a potential cause of the disease. These groups are referred to as study cohorts, where one is the exposed cohort and the other is the unexposed, or reference cohort. Usually, the investigator starts out with just one cohort, heterogeneous with respect to the exposure, and eventually defines subgroups (or cohorts) with differing exposure statuses. Thereafter, the cohorts are followed up or traced over time regarding the occurrence of the outcome. Advantages of the cohort design include a low risk for selection bias and the ability to take into account temporality; the exposure always precedes the disease. Disadvantages of the cohort study consist mainly of high costs and logistic difficulties in tracing the cohort members. Failure in the latter, i.e. loss to follow-up, is in fact the major source of bias in cohort studies.

Studies I-III were cohort studies, in which the aforementioned occurrence of disease was replaced by the outcomes HRQL and morbidity, and surgical factors were defined as exposures; different levels of exposure, e.g. hand-sewn and stapled anastomosis as well as low- and high-volume surgery, delineate subgroups within the cohort.

Cross-sectional studies

Cross-sectional studies are "studies that include as subjects all persons in the population at the time of ascertainment or a representative sample of all such
persons, selected without regard to exposure or disease status”. A cross-sectional study devised to estimate prevalence is called a *prevalence study*. The main advantages of the cross-sectional type of study are the ease and the low cost. Disadvantages comprise the difficulty in establishing temporality and causality, i.e. the time order of exposure and disease and the question of whether one event really led to the other.

Study IV focused on the incident cancer cases in Sweden for each year of study (1970-2006), but included all inhabitants each corresponding year. The exposure, age and sex, was ascertained in the population at the same time as the information on a cancer diagnosis was collected. In that sense, the study was based on consecutive cross-sectional data. Nonetheless, the population in each calendar year was defined as a cohort on its own, where it was assumed that the participants would be followed up during one study year and that the disease would have its onset at the end of that very year.

Study V is designated a cross-sectional study, in the sense that the exposures (risk factors for oesophageal adenocarcinoma) and the outcome (sex) were assessed at the same point in time. However, the data cannot be truly considered as cross-sectional, as the outcome was in fact established before the exposure. One might criticise the use of gender as an outcome, as this could hardly be deemed an event or a disease. On the other hand, the study was designed to evaluate associations between risk factors and gender, using relative risk measures (in this case, ORs) to allow adjustment for confounders; the study was naturally not devised to evaluate the risk of becoming male, but rather to determine the strength of the association of gender with certain exposures.

**Validity**

The end product of any epidemiological study (including design, conduct and analysis) is an estimate. This estimate may be more or less accurate, as influenced by estimation errors. These are classified as either *random* or *systematic*, where the latter type of error is also known as bias. The opposite of bias is termed *validity*, and an estimate free of systematic error may be defined as valid. The term is further broken down into *internal* and *external* validity. Internal validity corresponds to accurate measurement of study effects apart from random variation, and is considered a prerequisite for external validity, i.e. the generalisability of the findings to other populations. Random error, on the other hand, is antonymous to *precision*; precise estimates are associated with little random error.

Bias is often classified into three categories: *selection bias, information bias*, and *confounding*. 
Selection bias

Selection biases are due to procedures used to select subjects and factors that influence study participation. The relation between exposure and disease may be different for those who participate and those who do not, among the subjects eligible for study. The observed effect estimate may be a product of both the factors that determine the outcome and those that influence participation, as the estimate is based on participants. As the association between the exposure and the disease is usually unknown among the non-participants, the occurrence of selection bias is therefore often inferred rather than observed.223

Surgical research in general is often afflicted by selection bias, and oesophageal cancer surgery even more so. This is because oesophagectomy is relatively infrequent compared to other procedures, it is usually performed in specialised institutions, and patient follow-up may pose a major problem as a result of attrition. Most of the surgical literature concerning oesophageal cancer surgery is based on single-institution or hospital-based studies, where referral patterns and local tradition introduce selection and also make comparisons with other populations difficult (see below on generalisability). In contrast, the surgically oriented studies I-III described in this thesis, as they are based on the nationwide SECC register, can be said to be of population-based design. This requires full coverage of cases occurring in the population being studied during the given time period. The population-based design allays concern about selection bias, since theoretically there is no selection if the degree of participation is complete, even though such participation is virtually impossible to achieve. The participation rates in studies I and II were comparatively good (80%) – non-participation was mostly due to administrative problems, i.e. delayed registration, but also to unwillingness to participate. The former reason is not likely to be related to the exposures or the outcomes, whereas the latter may be associated with both and theoretically does threaten some of the internal validity of the studies. Nonetheless, the reason for this particular type of non-participation was infrequent (5%) and the possibly introduced bias is therefore probably negligible. It must be noted, however, that out of the 609 registered patients, only the 446 with R0 resection and still alive at 6 months were eligible for study. A low surgery volume220, 228, 229 in particular, but also technical surgical complications,140, 141, 149 have previously been found to be associated with an increased risk of postoperative death and this may have introduced selection bias, as it is not unreasonable to believe that the HRQL in the patients who died before 6 months would have been lower than in those who survived. Thus, the HRQL in the low volume categories and among the patients that suffered from surgical complications might have been artificially bolstered. Study III, on the other hand, used all the cases in the SECC register, which during the study period included as many as 90% of all operated patients, and the risk of selection bias was therefore further reduced.
Studies IV and V were also population-based in design: study IV used the Swedish Cancer Register, which had excellent completeness (98%) concerning the registration of oesophageal and cardia cancers; study V used the RP study data base, in which the participation rate was good (71%), albeit not excellent, and the risk of selection bias cannot be ruled out. Non-participation is especially a concern regarding the younger study population, where non-participation was admittedly higher, and the effect estimates among the subjects below 65 years of age may be biased in an unknown direction.

In summary, the high degree of participation and the population-based design of all the studies in this thesis should reduce selection bias to a minor problem.

**Information bias**

If the information collected about or from study subjects is erroneous, information bias, also known as *misclassification*, may arise. Misclassification regarding either exposure or outcome can be *differential* or *non-differential*. The misclassification is differential if it differs in degree between subjects with and without the outcome because of their outcome or their exposure. Differential misclassification may lead to unpredictable distortions of the risk estimates in either direction. Non-differential misclassification, on the other hand, is unrelated to the exposure and outcome status of the subjects under study; this type of bias is an inherent factor of all epidemiological studies, as it is a product of random error. Fortunately, the effects of non-differential misclassification are predictable: the observed effects are diluted and risk estimates tend to approach the null hypothesis. Nevertheless, this poses a problem when negative results are obtained, especially if study power is in question.

In studies I-III, the prospective design mitigated problems with differential misclassification, as the outcome status was not known prior to the exposure assessment. The medical records were retrieved through a project co-ordinator and subsequently the exposure and outcome information was extracted by the means of a structured protocol with predefined variables. These procedures reduced the risk that the participating hospital departments would introduce selective reporting of patient data and further ensured that classification and categorisation were uniform for all study variables. The use of extensively validated HRQL questionnaires was also a strength concerning information bias in studies I and II. Moreover, the patients completed the questionnaires on their own and were not in communication with operating surgeons or other staff members while responding to the questions, which otherwise would have raised concerns of study objectivity. In study III, the absence of self-reported complications from the hospital departments was a particular strength, as these in lieu of an independent assessment would be especially prone to selective reporting. However, as the results in this study were negative, the impact of non-differential misclassification might have played a role, which nevertheless should have been
mitigated by the structured recording of complications. Finally, the choice of surgery volume cut-offs in studies II and III could have influenced the estimated effects. The cut-off points were based on previous research and were, most importantly, made à priori, not letting the observed data generate thresholds which could have introduced spurious results. A different choice of cut-off might nonetheless have produced different results.

In studies IV and V data were collected retrospectively, which in theory may have introduced information bias (see discussion on retrospective study design). A more salient concern is raised by the possible misclassification of the cancer diagnosis in study IV. Although the completeness of registration is impressive (98%), misclassification concerning oesophago-gastric cancers is substantial, which certainly introduces bias. The observed effects concerning gastric cardia adenocarcinoma are probably a mix of true effects from the oesophageal, cardia and proximal stomach subsites. Moreover, in the elderly, bias might have been introduced by decreasing diagnostic effort or competing causes of death: the first should be non-differential regarding sex, while the second possibility could confer differential bias concerning the exposure, i.e. gender, as men tend to die younger. However, if this had materially affected the sex ratio decline seen in oesophageal adenocarcinoma with age, the same phenomenon would have been detected for all adenocarcinoma types. In study V, the risk of misclassification constituted a problem concerning the exposure variables. Even though the questionnaire was validated, it was evident that some questions, e.g. concerning NSAID use, raised classification difficulties and it is hard to assess whether or not the outcome (gender) was related to these problems.

Confounding

Confounding, or the confusion of effects, is of central importance in all epidemiological research, especially in observational studies. A confounder is an extraneous factor that is responsible for an outcome difference between the exposed and the unexposed. The confounder must be associated with both the exposure and the outcome; additionally, the confounder’s association with the outcome must be present apart from its association with the exposure. It is also termed extraneous, as the confounding factor may not be part of the causal pathway between the exposure and the outcome.

To demonstrate the actions of a confounder, one could choose the arguably most ubiquitous confounding factor in human studies, namely age. Exemplifying with variables pertinent to this thesis, the relationship of age to the exposure and the outcome is illustrated in Figure 12.
The potential confounder age is associated with the occurrence of complications (the exposure) as well as a low physical function (the outcome).

In this example, the confounder age is potentially related to surgical complications, as older patients are less resistant to surgical trauma and on average recover less successfully. Age is further associated with low physical function, a more or less natural consequence of advancing age. It is not, however, in the causal pathway, as surgical complications do not cause ageing, at least not in a chronological sense. The above reasoning forms the basis for the adjustment for covariates used in most studies in this thesis, as these covariates might be confounding factors and may therefore contribute to a mixing of effects.

In order to control for potential confounding, the methods of stratification and multivariable linear and logistic regression analyses have been employed. Adjustments by multivariable regression were used in studies I-III and V regarding, for example, age, sex, tumour stage, and operation type. Stratification was used mainly in studies IV and V, in order to separate effects of age and sex. In general, confounding was taken into account fairly well in the studies comprising this thesis; however, there is always the threat of residual confounding: unmeasured or unknown variables might bias the results, as well as confounding within strata, e.g. when categorisations have been devised too broadly. This might have been of particular concern in study V, where the study hypotheses required that the exposure categories were broadly defined in order to preserve sample size for adequate analyses.

**Generalisability**

Generalisability is the external validity of the conclusions drawn in a study, i.e. how well the observed findings can be transferred to other populations. The internal validity of a study carries markedly more importance when study accuracy is being evaluated, and there is usually good reason to only prudently extrapolate results from single studies, especially to other populations.

The source population used in studies I-III, i.e. almost all Swedish patients who underwent resection for cancer in the oesophagus or the gastric cardia, is comparable to patients of other European countries, as the demographics, diagnostics and treatment must be considered equivalent in most developed Western nations. Nevertheless, it is harder to justify comparisons with series of
patients at referral institutions, where selection bias might be pronounced. Noting that only 446 of the original 609 patients were eligible for study at 6 months in studies I and II, questions might be raised concerning the external validity of these studies. These concerns, however, are mostly related to attrition and are shared with all studies on the subject.

Likewise, study IV employed a national cancer register with near-perfect completeness; on the other hand, one may not be able to generalise the results from this study to people of non-Caucasian or even non-Nordic ethnicity, given the known differences in oesophageal adenocarcinoma incidence by race and ethnicity. In the chosen time periods, the Swedish population would still be considered ethnically homogeneous regarding cancer incidence. The same reasoning may be applied to the results of study V, where a random sample of the Swedish population was drawn.

To summarise, the generalisability of the studies of this thesis should be good in view of the population-based nature of all studies, but the results may not be entirely applicable in non-Western settings.

Precision

Precision, the influence of random error or chance, is reflected by the size of confidence intervals and p values. Stating a 95% level of confidence denotes that if the study were to be replicated numerous times, the CI should include the correct point estimate 95% of the time. The p value, which is derived from the same equations as the CI, is used for hypothesis testing and decision-making. Assuming that the null hypothesis, i.e. the statement that no relation between exposure and outcome exists, is true, the p value represents the probability of observing as strong an association as was actually observed or a stronger one. However, both the CI and the p value assume the absence of systematic errors, and must be interpreted with caution. At best, they provide a rough estimate of the statistical variability in the data and a measure of consistency between the data and the null hypothesis, respectively. Moreover, precision increases along with sample size, and consequently CIs become narrower and p values lower.

Type I error

A type I error occurs when the null hypothesis is rejected even when it is true. In other words an association between exposure and outcome appears to be statistically significant, when in reality no such relationship exists. The probability of committing such an error corresponds to the level of significance (α).

In studies where multiple analyses are made, the type I error may pose a major threat, as one association out of every 20 is a spurious result at the commonly used 5% significance level. In the studies in this thesis, this issue of multiple
testing was treated by predefining analyses as far as possible and restricting the number of tested hypotheses. For instance, only clinically relevant mean score differences were tested for significance in studies I and II. However, the number of significance tests performed in these studies was still quite large; the main positive finding that surgical complications reduce HRQL was still consistent over most scales, and would therefore be unlikely to be due to chance. Moreover, study III included quite a few hypotheses pertaining to different categorisations of the exposure (surgeon volume) and the outcome (complication groups), and in particular the scattered findings among the individual surgeons may have been due to chance and must be considered exploratory in nature. This also holds true for studies IV and V, where an abundance of tests were conducted.

**Type II error**

A type II error occurs when the null hypothesis is not rejected even though it is false. Thus, no statistically significant association is found, even though such a relationship exists. The probability of committing a type II error corresponds to the complement of the statistical power (β). The power of a test is the ability to correctly reject the null hypothesis and is determined by 1 - β. An often used level of power is 80%, i.e. one accepts that one test out of five will not detect a true association. A type II error may arise as a consequence of poor exposure and outcome data, or an inappropriate study design. The most common reason, however, is an insufficient sample size.

As most of the hypotheses in studies I-III were not corroborated, i.e. the respective null hypotheses were not rejected, the results from these studies were mostly negative. However, this may in turn have been due to the presence of type II error, and this needs to be investigated. The strict application of clinical relevance as a criterion for conducting statistical testing restricted the number of analyses, and from a statistical perspective no statement about whether the power was sufficient can actually be made. However, regarding some of the surgical factors that were evaluated, e.g. lymphadenectomy, type of anastomosis, bleeding, or surgical approach, the sample size was generally quite large and the mean score differences were far from reaching clinical relevance. The finding that these differences were small in the unadjusted comparisons may in theory have been due to confounding, but experience from the multivariable model regarding the tested associations indicated that observed differences were indeed attenuated, not increased. Thus, these negative results are likely to be true. The above argument also applies to study II.

In contrast, some of the other negative results in study I may have been due to insufficient power. For instance, the clinically relevant unadjusted difference concerning surgical approach and dyspnoea proved to be non-significant after adjustment, but with a power of 62%. On the other hand, the non-significant difference concerning coughing was established with a power of 98%.
Furthermore, the negative findings on the proximal resection margin, type of substitute, and duration of operation were hampered by small sample sizes (post hoc power estimations in the range of 10 to 66%). For comparison, the positive findings concerning surgical complications and several HRQL scales employed tests where the power was in the range of 87 to 99%.

In study III, post hoc power analyses revealed that the complication frequency differences between the surgeon volume categories would have had to be much larger than the observed ones to actually state that there were any differences statistically. This was not the case, as the complication frequencies seemed to be roughly equal. Thus, one could rest assured that if differences did exist, they were likely to be so small that they would be clinically negligible on a group level.

In study IV, several of the younger age strata included few female cases and consequently the CIs were wide. Thus there is a large degree of uncertainty concerning the sex ratios at younger ages for both gastric cardia and oesophageal adenocarcinoma, but especially the latter.

In study V, the power was generally good on account of the large sample size. However, the more exploratory analyses that evaluated risk factor clustering suffered from limited power due to stratification. This also held true for the age-stratified analyses, but to a lesser extent.

**Health-related quality of life measurements**

In this research, HRQL questionnaires developed by EORTC were used. This choice of questionnaires was based upon the fact that the core questionnaire has been developed for cancer patients, a particular oesophageal-specific module is available, both questionnaires have been well validated, and their widespread use in Europe facilitates interpretation and comparison of study results.

**Questionnaire adequacy and scoring**

The EORTC questionnaires, like many others, make use of categorical ordinal data. These contain a limited number of ordered responses with descriptive labels, e.g. 1) "not at all", 2) "A little", 3) "Quite a bit", 4) "Very much". Responses in a multi-item scale, which includes several items are included that measure the same aspect, are summated to yield a score. The multiple item scales improve reliability, as random errors tend to average out and any individual misclassified response would be less influential. Both of the EORTC questionnaires used include several multi-item scales, but some of them have only two items each, which may introduce an element of random error. Furthermore, it must be noted that both questionnaires, especially OES18, include several single items as well, making them even more prone to misclassification. Nevertheless, both questionnaires have been tested for validity and reliability, with satisfactory
In accordance with recommendations regarding analyses, the EORTC scoring manual was followed and the ordinal responses were linearly transformed to a score ranging from 0 to 100. The scaling technique is based upon the widely applied Likert method of summated scales, in which items within each scale are simply summed. When single items are transformed, the resulting scores retain the original categorical nature. However, when multi-item scales are formed, this nature is distorted, and several assumptions about the nature of the items are made. For example, it is assumed that it is appropriate to give equal weight to each item, and that each item is graded on a linear or equal-interval scale. Both these assumptions are questionable, and one might consider more sophisticated scaling and scoring procedures. Concerning weights, it has been shown that simple linear scoring systems are robust to most violations.

Clinical interpretation

The interpretation of HRQL mean scores is a complex matter. First, it has to be realised that even though items might be linear enough for statistical procedures such as linear transformation, the resulting scales are seldom linear in nature. For example, when comparing the proportion of patients able to walk a block with the scores of a physical function scale, mean scores of 40, 50, 60 and 70 corresponded to 32, 50, 80 and 90% of the patients. Thus, an improvement of 10 in this scale may signify different magnitudes of actual change at different ends of the scale. It has also been shown that reductions and improvements are perceived differently, and it has been suggested that patients are more sensitive to a change for the better than the other way around. Second, using a cut-off of 10 as clinical relevance concerning mean score differences ignores the distribution of the results. For example, if a difference from baseline of 5 is detected, the reason for this could be that 50% of the patients have a 10-point difference, while the other half have no benefit at all. In fact, the number needed to treat in this case to achieve a clinically important difference would be only 2 (absolute difference 50%), even though no clinically relevant mean score differences had been observed. This approach was unfeasible, however, in studies I and II, as baseline measures were not collected, and the proportion of patients that would be affected could not be calculated. Instead, we presented 95% CIs to suggest the patient distribution and give an idea of how the group as a whole differed according to the exposure.

Moreover, there are inherent problems with baseline assessments, especially in the context of surgical oncology. These need to be collected after the diagnosis has been made, when the tumour will already have influenced the patient’s
HRQL. The magnitude of this impact may be highly variable according to the tumour behaviour and non-measurable patient characteristics, and a true baseline, i.e. the HRQL status before tumour appearance, is virtually impossible to retrieve.\textsuperscript{175}

The absence of baseline values may, however, lead to other problems. The HRQL estimates made 6 months after surgery could represent a mix of effects, where one component could be deviating baseline values, and another the effect of the evaluated exposure. This would constitute confounding, and may in theory either attenuate or augment differences. By adjusting for factors highly pertinent to HRQL differences, e.g. age and sex,\textsuperscript{221} as well as potential surgical covariates (tumour, clinical and surgical parameters), the risk of this particular type of confounding was nonetheless reduced.

The definition of clinical relevance used in this thesis has considerable support in the literature, as already discussed (see appropriate section in Background). Multiple studies, using anchor-based as well as distribution-based methods, have confirmed the appropriateness of 10 as a sufficiently large mean score difference to be pertinent, while simultaneously reducing falsely positive results.\textsuperscript{152} However, this difference needs to be understood in context, where comparisons with clinical parameters might provide some insight. For instance, King\textsuperscript{167} synthesised data from several studies using the EORTC QLQ-C30, and found that a mean score improvement of 10 would represent considerable symptom control, and a reduction or reversal of weight loss. Concerning oesophageal cancer patients, Blazeby \textit{et al}\textsuperscript{234} found differences of approximately 20 regarding functions and symptoms between patients treated with a curative intent and those that were in a palliative stage; our research group claimed mean score differences concerning QLQ-C30 and QLQ-OES18 of about 10 to 20 between patients who had undergone a macroscopically radical resection and those that were not free of residual disease\textsuperscript{96}; likewise, a weight loss of >20\% postoperatively was associated with mean score differences ≥10 after oesophagectomy\textsuperscript{235}; finally, such differences were also found between patients who were diagnosed with stage III and IV tumours, of whom half of the former were operable, whereas almost none of the latter underwent surgery.\textsuperscript{158} Although a number on a numerical scale might be hardly considered to be intuitively understood by patients and clinicians, examples like these may facilitate interpretation of what constitutes a clinically relevant HRQL difference.

Lastly, the timing of the HRQL assessment in studies I and II deserves some commentary. As already noted, most acute symptoms have subsided 6 months after oesophagectomy,\textsuperscript{12, 176, 177} but some HRQL reductions remain and there are some data stating that the full recovery may take up to a year.\textsuperscript{11} Hence, a different choice of time point for the HRQL assessment might have yielded different results. However, this specific time window was deliberately chosen in
order to evade the possibility that tumour recurrence might influence the HRQL outcomes in an unpredictable way, as this is difficult to adjust for; in a 6-month time window, only 8.5% of R0 have been diagnosed with a recurrence, as compared to 12.5 and 25.6% after 9 and 12 months, respectively.216

FINDINGS AND IMPLEMENTATIONS

Surgical complications influence health-related quality of life

The findings in study I suggest that wider resection margins, more extensive lymphadenectomy, a longer operation time and a transthoracic approach are not measurably deleterious to HRQL 6 months after oesophagectomy for cancer. Moreover, no differences concerning type of anastomosis could be found. On the other hand, technical surgical complications had a clinically relevant and long-standing harmful effect on several HRQL aspects.

Few other studies have focused on surgical technique. In a rare randomised clinical trial, physical symptoms 3 and 6 months after surgery were significantly improved in patients who had a transhiatal resection compared with patients operated on with a transthoracic approach.178 A few study differences may, however, explain the differing results with respect to study I: first, the clinical trial did not include type III cardia tumours; second, transhiatal surgery in Sweden is mainly conducted in the standard way, but is often done through an abdominal only approach, with the anastomosis made in the hiatus rather than in the neck. Another research group compared transthoracic oesophagectomy with total gastrectomy in oesophago-gastric junction tumours (type I-III cardia tumours), and claimed a greater HRQL deterioration from baseline values in the first group.236 However, the patients that were selected for total gastrectomy had type III tumours only, and also had worse baseline HRQL values – response shift may have been responsible for some of the observed differences. Furthermore, data from a Dutch trial comparing transthoracic and transhiatal surgery suggest that survival is better when the former approach is used for type I tumours.112 Nevertheless, any HRQL differences between the two approaches seem to be transient, as shown in the aforementioned trial178 and supported by a recent study with a 5-year follow-up, where no disparities relating to surgical approach could be found.175

In two trials, in which validated HRQL questionnaires were not used, hand-sewn cervical anastomoses were compared with stapled intrathoracic anastomoses, and patients reported dysphagia to a similar degree in both groups up to a year after surgery.237, 238 This result corroborates the findings in the current study that the type of anastomosis does not matter from an HRQL perspective.
The finding that surgical complications lead to HRQL reductions is supported by the few studies addressing this subject. In a single-institution study it was found that the occurrence of anastomotic insufficiency postoperatively entailed worse physical function after 2 or more years. Our research group has previously results similar to those in study I, but based on a smaller number of patients from the same surgical register.

The impact of surgical complications on long-term HRQL demands commentary. Postoperative complications such as anastomotic insufficiency, necrosis of the substitute and gastric perforation are all major risk factors for serious infection; moreover, thoracic duct injury may lead to chylothorax and recurrent nerve injury can cause chronic speech difficulties and aspiration, whereas major bleeding often requires reoperation. In most instances, however, complications have a physiologically short duration, but nevertheless they seem to influence HRQL at distant points in time. First, there is a possibility that response shift is involved, i.e. the patient's assessment of his or her HRQL might change on the basis of the treatment experiences and expectations; thus the rough postoperative course experience by patients with severe complications may induce a different perspective of HRQL regardless of the underlying biophysiological condition. Second, surgical complications may in reality delay recuperation or induce changes that permanently alter physiology. Third, a common cause may be involved: it has been suggested that micrometastases present preoperatively might affect HRQL and also predispose to complications. However, there is still no evidence that preoperatively poor HRQL predicts complications. Furthermore, complications are not convincingly linked to worse survival, which should be the case if micrometastases, which would affect the prognosis, caused both complications and worse HRQL. With the above reasoning and since the findings in study I were adjusted for co-morbidity, tumour stage, age and sex, for example, i.e. factors that would influence HRQL, it still seems more likely that the complications themselves are causal factors. Finally, it must be noted that the findings on surgical complications at 6 months may be temporary, as a different choice of time window might have produced different results. Nevertheless, there are grounds to believe that changes at 6 months linger on, as it has been shown that HRQL reductions at that time point in oesophageal cancer survivors persist at 3 years.

In conclusion, there are no grounds from an HRQL perspective to refrain from more extensive surgery, if this does not mean that the risk of surgical complications increases. With this information, surgeons may strive further to develop oncologically more radical surgery, while paying attention to minimising techniques and situations leading to possible complications.
Surgery volume does not influence health-related quality of life

Study II did not reveal any HRQL benefits among oesophageal cancer patients who were operated on at HVHs or by HVSs. Moreover, there were no marked HRQL differences between patients of individual HVHs.

The current paper is allegedly the first to address the role of oesophageal cancer surgery volume in relation to HRQL outcomes. However, it has previously been shown that high-volume surgery lowers postoperative mortality, while the complication rate may also become lower. The latter would therefore confer HRQL reductions, as suggested in study I and in a pilot study using a subset of the patients included in study II. Nonetheless, the hypothesis that high-volume surgery results in better HRQL was rejected. This finding was indeed in line with the aforementioned pilot study, where university clinic treatment did not prove to be superior in this respect.

Contradicting the study hypothesis, patients operated on by HVSs seemed to have more problems with coughing. As there is no apparent biological reason for this finding and no other differences were found, it may have been due to chance. The same interpretation could be drawn regarding the seemingly scattered findings between individual HVHs.

Overall, no beneficial effects of high-volume surgery on later HRQL outcomes were found, which deserves some specific commentary. The classification of surgeon volume may have played a role, as the case load allocation method ensured that the skill and supervision of the senior surgeon were taken into account; however, senior HVSs may also be more involved in training than senior LVSs, and therefore the former could have been fraught with more complications, which, as shown in study I, leads to HRQL reductions, possibly counteracting any positive effects of high-volume surgery. Nevertheless, using only the primary operator as the main variable would underestimate the impact of senior advice and immediate assistance. There is also the possibility of confounding from the unmeasured variable experience in other areas of advanced surgery, as only oesophagectomies were taken into account.

The lack of findings with regard to HRQL must also be considered in relation to other pertinent data, especially those for long-term survival. The literature concerning high-volume surgery and prognosis is not only sparse but also conflicting, with population-based studies that show no material differences and studies that do suggest better survival in HVHs, but inadequately adjusting for tumour stage.

In study II performance of high-volume surgery showed no advantages from an HRQL perspective. These results, however, do not rule out possible differences
between surgery volume groups concerning other relevant outcomes, such as postoperative mortality, incomplete resection, and early tumour recurrence. Therefore, high-volume oesophageal cancer surgery should continue to be recommended.

**Surgeon volume does not equate with skill**

The findings in study III suggest that surgeon volume has no influence on the risk of technical surgical complications occurring within 30 days of oesophageal cancer surgery. There is some evidence, however, of substantial variation in complication rates among individual HVSs.

While the risk of postoperative mortality has previously been shown to be reduced in high-volume surgery, complications as a primary outcome have rarely been assessed. Our research group has previously published a study incorporating about half of the patients in study III, but evaluated a number of hypotheses and used a slightly different cut-off for surgeon volume. That previous study showed a higher risk of anastomotic leakage among patients, who were operated on by surgeons performing fewer than 5 oesophagectomies per year; the apparent disparities between the studies may, however, be explained by enhanced sample size and reduced risks of chance error from multiple testing in study III. A recent retrospective study from Japan with voluntary surgeon participation showed a halved risk of postoperative complications in HVSs compared to LVSs (>100 compared to <49 operations ever, respectively), but these findings must be interpreted cautiously as the study design was markedly inferior compared to that of study III, and complication definitions were absent.

Research concentrating on hospital volume and morbidity is more abundant. A national study from the US showed a lower frequency of undefined surgical complications in HVHs (10%) than in LVHs (12%), which amounted to a statistically non-significant 30% risk reduction, though with no adjustments, for example, for tumour stage and radicality. In a study limited to Maryland, a statistically significant 3-fold risk increase was found, however, in LVHs. These findings are contradicted by a British audit evaluating oesophago-gastric cancer surgery, where no association between hospital volume and risk of surgical complications was found; these complications were defined similarly to those in study III. These findings were corroborated by another recent study from the UK, also using a population-based design. It must nevertheless be noted that all the above studies claim worse mortality rates in LVHs, and one explanation for this finding despite equal complication rates might be better management of these complications. Finally, it is wise to be prudent when comparing results in the literature, as differing definitions of both volume and complications abound, as well as considerable publication and selection bias.
In study III no differences were found between volume categories, which could be due to information bias, as explained above concerning study II. This problem, however, is almost uniform in surgery volume research. Furthermore, as the volume-outcome relationship is incompletely understood, other researchers may have ignored problems with reversed causality, where centres with preferable outcomes attract more referrals, thus augmenting the case load of such institutions as a product of good results. Individual HVSs displayed major differences in study III, which would be an interesting venue for further research; larger studies concerning other oncological procedures have also verified significant differences among HVSs.

Reasoning as in study II, study III does not in itself provide support for low-volume surgery, despite the lack of a proven association with morbidity. There are still good grounds to centralise oesophageal cancer surgery on the basis of the established relationship to reduced postoperative mortality, but it is still evident that further research is warranted in attempts to prevent surgical complications. It does seem that high-volume surgery in itself is not the key factor, but factors independent of case load might prove to be more important.

The oesophageal adenocarcinoma sex ratio is age-dependent

Study IV indicated that the strong male predominance of oesophageal adenocarcinoma decreases steadily with increasing age. The pattern for gastric cardia adenocarcinoma is more consistent between age groups, and displays a less pronounced male excess.

The à priori hypothesis stated that the pattern of age-dependency would reflect a protective oestrogen effect, in the form of 1) a delay in the onset of disease in women, and 2) a constant male predominance up to the female menopausal years, after which it would decrease. These phenomena were not evident in the data, thus not providing support for the hypotheses. Instead, the male predominance decreased steadily with advancing age, and the incidence curve modelling rather conveyed the message that female incidence never reached the same slope as the male counterpart. In fact, the pattern for gastric cardia adenocarcinoma showed more consistency with the hypothesis, but these results may be the product of oesophago-gastric junction misclassification, thus making any conclusions difficult to draw.

In an analogous study from Scotland it was concluded that the male predominance of upper gastrointestinal adenocarcinoma is in general due to a delayed cancer development in females prior to the ages of 50-60 years. However, there is not much aetiological common ground to defend the merging of adenocarcinomas of the distal stomach, the gastric cardia and the oesophagus. Taking into consideration the data on the latter type only, a strikingly similar
pattern to the one found in study IV was revealed.\textsuperscript{199} Admittedly, both studies suffer from limited power due to fewness of young female cases, and any interpretation must be made with caution. There is nonetheless independent support from a large American study using register data, where a similar steady sex ratio decline with age was observed concerning oesophageal adenocarcinoma.\textsuperscript{19}

Evidently, male oesophageal adenocarcinoma has an earlier onset than the female counterpart, and it seems that women never quite reach the male incidence rise with age. These findings would reasonably be reflected by an early male onset of known (or unknown) risk factor exposures, of which reflux disease and obesity are likely to be important. Indeed, the prevalence of these risk factors at a young age is higher among men than among women in population-based studies.\textsuperscript{189-191} which might provide a link. Furthermore, as previously elaborated (see Background), male-type obesity has been shown to be an independent risk factor for oesophageal adenocarcinoma,\textsuperscript{42} and reflux disease in men might more often be of the erosive and more carcinogenic type.\textsuperscript{185} The findings in study IV are not in line with a major role for oestrogen in adenocarcinoma development, results that are consistent with negative findings concerning childbearing\textsuperscript{201} and hormone replacement therapy,\textsuperscript{202} while there are conflicting results regarding the presumed lower incidence of oesophageal adenocarcinoma due to oestrogen and anti-androgen therapy in prostate cancer cohorts.\textsuperscript{203, 208}

The results of study IV need to be corroborated in further research, notably including more female cases to lessen uncertainty in the younger age strata. The study, however, provides no support for the role of oestrogen in adenocarcinoma development. It seems more likely that the reason for the male predominance is linked with other differences between men and women than hormonal exposure only.

**Risk factors do not explain male predominance**

Study V suggests that exposure to risk factors for oesophageal adenocarcinoma is more common among men than among women in the general population. Each of the risk factors high BMI, tobacco smoking, and low socioeconomic status were more common among men, and use of NSAIDs was less prevalent among men. However, reflux symptoms were consistently more common in women. Combinations of these risk factors were not materially more prevalent in men, except when NSAID use was included. Age-stratified analyses indicated that a high BMI was more common in men at a younger age.

As this is the first study of its kind in which most of the known risk factors were evaluated simultaneously, comparisons with other studies are difficult. There
are, however, other population-based studies claiming that while reflux is not more prevalent in men,\textsuperscript{189, 190} a high BMI is\textsuperscript{191, 192} Tobacco smoking is also more prevalent in men,\textsuperscript{193} while at least aspirin use seems to be more common in women.\textsuperscript{195} Thus, for each risk factor there is some independent support for the distribution shown in study IV, where the multivariable regression mostly favoured a higher prevalence in men, but to a minor degree.

If the observed male predominance in oesophageal adenocarcinoma were to be explained by differences in risk factor exposure, the results of study V would hardly account for the aforementioned high sex ratio, especially as the combination of the main risk factors, reflux and a high BMI, did not prove to be more common in men. However, as elaborated earlier (see Background), these risk factors may have a differential impact according to gender. Some data show that the carcinogenic erosive-type reflux disease is more common in men,\textsuperscript{185} while a high BMI in men may be more associated with adenocarcinoma than in women.\textsuperscript{18, 34, 197} Concerning the latter, conflicting evidence is nevertheless available.\textsuperscript{198} Moreover, male-type obesity with a large content of intra-abdominal fat seems to particularly increase the risk.\textsuperscript{42} There is also a possibility that more disputed and unmeasured aetiological factors for oesophageal adenocarcinoma, such as infection with \textit{H. pylori}, bias the results – this infection seems, however, to be at most slightly more prevalent in men.\textsuperscript{196}

Interestingly, there were some differences between the group aged over 65 years and the group that had younger participants, concerning male and female exposure. For example, it seemed that a high BMI was even more common in young men as compared to young women, than in older men as compared to older women. Some data state that especially young men are particularly prone to be harmed by a high BMI with regard to risk of adenocarcinoma,\textsuperscript{34} while there is increasing evidence that the male predominance in incidence is age-dependent, the difference being especially pronounced in the young.\textsuperscript{19, 199, 200} Thus, one may speculate that the age-stratified results in study V provide a link to the age-dependency.

Study V was not able to answer the question as to whether the male predominance is due to sex differences in the distributions of risk factors. Rather, it merely showed that there are differences, albeit small, among men and women, in risk factor exposure; these are unlikely to explain the male predominance in oesophageal adenocarcinoma. To more accurately respond to the first question, there is a need for continued research. More specifically, one would require a large cohort with valid measurements of all known risk factors and the outcome, oesophageal adenocarcinoma; one would moreover need to establish the independent association of sex with this tumour, including adjustment for all possible confounders. Only then could the predominance ascribed to male sex be fully estimated.
CONCLUSIONS

- Surgical technical complications have a detrimental impact on several aspects of HRQL in patients operated on for oesophageal cancer; other surgical factors, e.g. wider resection margins, surgical approach, operation time, perioperative bleeding, and extent of lymphadenectomy, do not seem to influence HRQL outcomes 6 months postoperatively.

- Hospital and surgeon volume do not influence the HRQL of patients undergoing oesophagectomy, as assessed 6 months after surgery.

- Surgeon volume is not associated with the occurrence of technical surgical complications in resection for oesophageal and cardia cancer. Individual HVSs, however, display striking differences in complication frequencies in unadjusted analyses.

- The incidence rate ratio in oesophageal adenocarcinoma between men and women is age-dependent: this sex ratio seems to be at its highest in the youngest age groups and consistently declines thereafter.

- The distribution of established risk factors for oesophageal adenocarcinoma differs between men and women in the general population, but only to a limited extent. Excluding differential NSAID use, there is no evidence of risk factor clustering in men, thus making it unlikely that the risk factor distribution itself could explain the male predominance in oesophageal adenocarcinoma.
The HRQL in oesophageal cancer patients is still severely compromised, even in survivors. The surgery itself is a major culprit, and this thesis has shown that technical complications, but not extent of surgery and surgery volume, worsen the situation even more. However, there is still a need to identify more surgical factors associated with HRQL, both in the short and the long term. Even larger studies, preferably with baseline HRQL values and of prospective and population-based design, are needed to adequately establish differences attributed to surgical technique. Of particular interest is the lack of association between surgeon volume and complications, while it is evident that complication rates differ considerably between individual surgeons with high case loads. Thus, there are probably grounds for improvement, though not necessarily related to increasing experience. Furthermore, the methodological research concerning interpretation and presentation of HRQL outcomes needs to be strengthened, as routine use in clinical practice still must be considered uncommon.

The striking male predominance in the incidence of oesophageal adenocarcinoma remains a mystery. This thesis adds to the literature by confirming the age-dependency of this tumour, while no clear support from the sex-specific risk factor distribution could be shown. Larger studies that recruit young female cases to a greater degree are required to establish the relationship to age, and would probably demand prospective cohorts of patients with adenocarcinoma precursors, such as Barrett’s oesophagus. Such a study, incorporating more data on risk factors and possibly molecular differences, might shed more light on the complex interactions between risk factor exposure and gender characteristics, such as hormones. Currently, we are planning a nested case-control study in a prostate cancer cohort, in order to elucidate whether treatment with anti-androgens may confer a reduced risk of oesophageal adenocarcinoma.
POPULÄRVETENSKAPLIG SAMMANFATTNING

BAKGRUND

Cancer i matstrupe och övre magmun är ovanliga cancertyper ur ett västerländskt perspektiv. Globalt sett är dock matstrups cancer den åttonde vanligaste cancerformen och ansvarig för vart sjätte dödsfall i cancer. Antalet insjuknande i den förre sällsynta tumörtypen adenokarcinom i matstrupen har under de senaste decennierna kraftigt ökat i USA och Europa, inklusive Sverige, och denna är nu dominerande. Sväljningssvårigheter och viktnedgång är ofta de första tecknen på matstrups cancer och signalerar ofta att sjukdomen är spridd. Matstrups cancer innebär totalt sett en femårsöverlevnad som är lägre än 16 % i västvärlden, och endast kirurgi varigenom alla rester av tumören avlägsnas erbjuder i nuläget en chans till bot; emellertid överlever på sikt knappt 40 % av de som opereras på dylikt sätt. Dessutom innebär operationen, som ofta inbegriper kirurgi i såväl bröst- som bukhålan, stora risker för komplikationer (26-41 %) och död (<5 %) i efterförloppet. Tidigare forskning har främst inriktats mot att förbättra överlevnaden, medan tillgängliga studier kring kirurgiska komplikationer och kirurgins påverkan på symtom och livskvalitet är fåtaliga. Den stora ökningen av insjuknande i adenokarcinom har till största del drabbat män och 7-10 gånger fler män än kvinnor drabbas av denna tumörform. Starka riskfaktorer för adenokarcinom innefattar refluxsjukdom (halsbränna och sura uppstötningar) och övervikt. En del forskning pekar på att det senare utgör en starkare riskfaktor för män vad gäller cancerinsjuknande. I denna avhandling undersöktes dels hur kirurgiska faktorer såsom operativ teknik och erfarenhet av kirurgi inverkar på symtom och funktioner på längre sikt, dels hur mäns och kvinnors insjuknande i adenokarcinom är kopplad till ålder och dessutom hur riskfaktorena för denna sjukdom är fördelade bland män och kvinnor. Det övergripande syftet var att förbättra den tillgängliga kirurgin för matstrups cancer och dessutom öka förståelsen för varför män och kvinnor drabbas i olika hög grad av adenokarcinom i matstrupen.

METODER

Avhandlingen består av fem delarbeten. I delarbete I till III användes data från ett svenskt kirurgiskt forskningsregister för matstrups cancer (SECC-registret), där 90 % av de patienter som opererats i landet från 2001 till 2005 finns registrerade. I detta register samlades kontinuerligt in uppgifter från journaler och tumörpreparatsvar om patient- och tumörkarakteristika, operationer, operatörer och komplikationer, vilka granskades av registerhållarna och undertecknad. För delarbete I och II skedde mätning av kvarvarande symtom
RESULTAT

Delarbete I och II

Patienter som genomgått operation för matstrups cancer och utsatts för kirurgiska komplikationer, exempelvis stor blödning eller läckage i skarven mellan magsäck och matstrupsrest, uppvisade kliniskt betydelsefulla och statistiskt signifikanta försämringar som ökad andfåddhet och trötthet, ökat illamående eller värre kräkningar, ökad hosta, nedsatt fysisk funktion och arbetsförmåga, försämrad social samvaro samt sänkt allmän livskvalitet. Inga skillnader kunde påvisas hos patienter som opererats på ett mer omfattande sätt, exempelvis med större lymfkörtelutrymning, större marginal av frisk vävnad till tumören, större mängd blödning, längre operationstid, eller kirurgisk öppning av brösthålan. Vidare kunde ingen skillnad ur ett livskvalitetsperspektiv skönjas mellan patientgrupper opererade av kirurkar med stor eller liten erfarenhet av matstrups cancer kirurgi, eller på sjukhus där många eller få operationer per år utfördes.

Delarbete III

Inom 30 dagar efter kirurgi för matstrups cancer drabbades 25 % av patienterna av någon förbestämd teknisk kirurgisk komplikation, medan medicinska komplikationer skedde i 35 % av fallen. Andelen som avled inom ovan tidsperiod var endast 3 %. De patienter som hade opererats av kirurkar med erfarenhet från många operationer (>6 per år) hade inte lägre frekvens av kirurgiska komplikationer än de som opererades av kirurkar med mindre erfarenhet (2 till 6 och <2 per år). Bland enskilda kirurkar som opererade många patienter per år noterades statistiskt signifikanta skillnader vad gällde frekvens av kirurgiska komplikationer i analyser i vilka hänsyn till påverkan från störfaktorer emellertid inte kunde tas.

Delarbete IV

För samtliga åldersgrupper var könskvoten mellan män och kvinnors insjuknande 5 till 1 för adenokarcinom i matstrupen och 4 till 1 för övre magmunn. Vad gäller matstrupe närmade sig könskvoten i de yngre åldersgrupperna 10 till 1, medan denna kvot avtog till knappt 4 till 1 hos de äldsta. Motsvarande könskvot för magmun var mer konsekvent 4 till 1 i de flesta åldersgrupperna, förutom i de äldre, där kvoten sjönk. Motsvarande KI för framförallt de yngre åldersgrupperna blev breda, eftersom det fanns få kvinnliga fall registrerade. Vidare kunde ingen effekt skönjas från uppdelningen i perioderna 1970-1986 och 1987-2006.
Delarbete V

Riskfaktorerna övervikt, rökning och inget bruk av antiinflammatoriska läkemedel befanns vara något vanligare hos män, medan refluxsjukdom snarare var mer frekvent i det kvinnliga urvalet. Inga markanta skillnader kunde stå att finna i utbildningslängd. När samtidig exponering undersöktes noterades inga samband till manligt kön, förutom när bruk av antiinflammatoriska läkemedel togs hänsyn till. Vidare visade åldersuppdelade analyser (65 år och yngre kontra äldre än 65 år) att sambandet mellan övervikt och manligt kön var mer uttalat hos de yngre.

SLUTSATSER

Omfattningen av kirurgi för matstrupscancer spelar mindre roll för patienters symtom och funktioner sex månader efter operation, medan förekomsten av kirurgiska komplikationer har kliniskt betydelsefull påverkan. Emellertid verkar inte antal operationer för matstrupscancer som genomförs på det opererande sjukhuset inverka på livskvaliteten och heller inte hur erfaren kirurgen är. Medan ej heller antalet operationer per år utförda av kirurger påverkar frekvensen kirurgiska komplikationer, finns betydande skillnader mellan enskilda kirurger. Könkvoten i insjuknande av adenokarcinom i matstrupe är starkt åldersberoende, vilket kan vara en ledtråd till den uttalade manliga dominansen i denna sjukdom. Slutligen finns vissa skillnader bland män och kvinnor vad gäller riskfaktorer för att utveckla adenokarcinom, men till så pass liten grad att det förefaller osannolikt att detta skulle kunna förklara diskrepansen i cancerinsjuknande mellan könen.
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