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Etiological aspects of gastroesophageal cancers - An epidemiological approach

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In the name of God

ABSTRACT

Aims: The aims of this thesis were to study the association of overall dietary habits, duodenal ulcer and gastric ulcer diseases, as two models of *Helicobacter pylori* (*H. pylori*) infection and the development of gastroesophageal cancers to further explore the etiology of these malignancies. Moreover, the association between parity, a proxy for high level of female hormones, and stomach cancer risk was studied to shed light on the enigma of male predominance in this cancer.

Methods: In a nationwide population-based case-control study in Sweden with 165 esophageal squamous cell carcinoma, 185 esophageal adenocarcinoma and 258 cardia cancer cases and 815 randomly selected controls we estimated relative risks associated with dietary patterns. Furthermore, cohorts of 61,548 and 81,379 unoperated patients with duodenal ulcer and gastric ulcer, respectively, recorded in the Swedish Inpatient Register since 1965, were followed and standardized incidence ratios were estimated for esophageal cancer by histology, compared with the Swedish general population. We also followed cohorts of 59,550 and 79,412 unoperated patients with duodenal ulcer and gastric ulcer, respectively, plus 12,840 patients with partial gastric resection and 8,105 with vagotomy, recorded since 1970. We estimated relative risks for stomach cancer by anatomical subtype compared to the Swedish general population for unoperated cohorts, whereas relative risks were estimated among operated patients relative to unoperated ones with the same ulcer type. Finally, in a case-control study, nested within a cohort of Swedish women born in 1925 or later, with 286 cardia cancer and 2,498 non-cardia stomach cancer as well as corresponding 1,430 and 12,490 controls, we investigated the relationship between parity and risk of stomach cancer by anatomic subsite.

Results: A "healthy diet" tended to moderately decrease the risk of esophageal and cardia cancers, "Western diet" increased risks of cardia cancer and esophageal adenocarcinoma, whereas a dietary pattern characterized by high beer and liquor intake significantly increased the risk of squamous-cell carcinoma of the esophagus. We observed that patients with duodenal ulcer had a significant 70% excess risk of esophageal adenocarcinoma, a non-significant small excess risk of esophageal squamous cell carcinoma, a halved risk of non-cardia cancer, and a risk of cardia cancer slightly above expectation. Gastric ulcer was unrelated to esophageal adenocarcinoma but linked to 80% increased risk of esophageal squamous cell carcinoma, and doubled risks for both anatomical types of stomach cancer. Duodenal ulcer patients who underwent gastric resection had a 60% risk elevation for non-cardia cancer compared to unoperated ones. Vagotomy was associated with a greater risk in the first 10 years, but this excess disappeared with further follow-up. Resected gastric ulcer patients had a 40% risk reduction for non-cardia cancer relative to their unoperated peers. We found no association between parity and risk of non-cardia stomach cancer comparing ever-parous women with nulliparous, whereas a statistically significant 30% risk reduction for postmenopausal cardia cancer was noted among ever-parous women relative to nulliparous.

Conclusions: Overall dietary habits seem to play an important role in the carcinogenesis of esophageal and cardia cancer. The well-established strong inverse association of *H. pylori* seropositivity and risk of esophageal adenocarcinoma does not pertain to all infections. The duodenal ulcer related protection against stomach cancer does not seem to affect cardia cancer. It seems that the pattern of stomach colonization and/or the clinical consequences in the stomach might play a pivotal role in the long term outcome of *H. pylori* infection. With gastric resection, risks are shifted toward normality, regardless of underlying ulcer type. Exposure to female sex hormones is not associated with protection against stomach cancer and does not seem to explain the male predominance for such cancer. However the observed moderate inverse relationship between parity and cardia cancer might be mediated by other factors than hormonal.

Key words: Nutrition, dietary patterns, factor analysis, esophageal cancer, stomach cancer, gastric, cardia, non-cardia, adenocarcinoma, squamous-cell carcinoma, duodenal ulcer, gastric ulcer, estrogen, parity, risk, case-control study, cohort study, nested case-control study, odds ratio, standardized incidence ratio

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III: **Bahmanyar S, Ye W, Dickman P, Nyrén O.** Long-term risk of gastric cancer by sub-site in operated and unoperated patients hospitalized for peptic ulcer. *Am J Gastroenterol* 2007; 102:1185–1191.

IV: **Bahmanyar S, Lambe M, Zendehdel K, Nyrén O, Boffetta P, Ye W**. Parity and Risk of Stomach Cancer by Sub-site; a Nationwide Study in Sweden. *Submitted*

CONTENTS

LIST OF ABBREVIATIONS

BMI	Body mass index
CagA	Cytotoxin-associated gene A
CI	Confidence interval
COX	Cyclooxygenase
DU	Duodenal ulcer
EAC	Esophageal adenocarcinoma
ESCC	Esophageal squamous cell carcinoma
GU	Gastric ulcer
H. pylori	*Helicobacter pylori*
HCl	Hydrochloric acid
NRN	National registration number
NSAID	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
RR	Relative risk
SIR	Standardized incidence ratio

1. Introduction

Esophageal cancer and stomach cancer are characterized by wide international variations. Esophageal cancer, with an estimated 462,000 new cases per year in 2002, is the eighth most common cancer.[1] Stomach cancer is the fourth most common cancer worldwide and the second most common cause of death from cancer. For esophageal cancer male to female ratio shows a wide variation in different geographic areas, whereas for stomach cancer the corresponding ratio is about two in most geographic areas.

During recent decades there have been dramatic changes in epidemiological characteristics of esophageal and stomach cancers.[1-3] The incidence of esophageal adenocarcinoma is increasing significantly whereas the incidence of esophageal squamous cell carcinoma, the dominant histological type, has been stable or slightly decreasing.[4] There has been a remarkable decline in the incidence of stomach cancer during the past 30-40 years driven entirely by a decrease in the incidence of non-cardia stomach cancer,[3] whereas incidence of stomach cardia adenocarcinoma has been stable or has increased moderately,[5] in Western countries. The reasons for these changes are yet to be found, but due to a notable decline in the *Helicobacter pylori* (*H. pylori*) infection rate [6] as well as an extraordinary change in the dietary habits of Western population,[3, 7-11] it has been suggested that there is an association between these factors and reported changes in epidemiological characteristics of upper gastroesophageal cancers.

This thesis investigated the association between dietary factors, *H. pylori* infection and parity, and the risk of esophagus and stomach malignancies in order to shed further light on the descriptive epidemiology and the etiology of these cancers.

2. Background

2.1. Function of the esophagus and stomach

The esophagus functions as a conduit that transports swallowed food from the pharynx to the stomach (Figure 1). Esophageal peristalsis causes the lower esophageal sphincter to relax. In the normal condition, the sphincter remains firmly closed in the absence of esophageal peristalsis to prevent reflux of the gastric contents into the esophagus which can lead to esophagitis. During swallowing, the esophagus causes the stomach to relax by a vagovagal reflex.[12]

The stomach has several essential functions and acts as a reservoir that allows the ingestion of a large meal which stays there up to 4 hours. Later, vigorous contractions in the antrum break the ingested items into smaller pieces and mix them with gastric juice, and in a controlled rate empties the chyme (partly digested food) into the duodenum. The stomach secretes several factors which are necessary for a normal function of the digestive system such as hydrochloric acid (HCl), pepsins, intrinsic factor, mucus and bicarbonate. HCl kills nearly all ingested pathogens; therefore those with low rates of gastric acid secretion due to disease or use of medications that suppress HCl secretion are more at risk of infection by ingested microorganisms.[12]

In a normal person the gastric mucosal barrier can protect the stomach even if HCl and pepsins are hypersecreted. However, the stomach is perfectly capable to repair epithelial damages. But any defect or suppression in the secretion of either bicarbonate or mucus might damage the mucosal surface by the effect of acid and pepsin. Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) inhibit secretion of both mucus and bicarbonate; therefore prolonged use of these drugs can result in epithelial surface damage and cause gastritis or even gastric ulcer.[12-14]

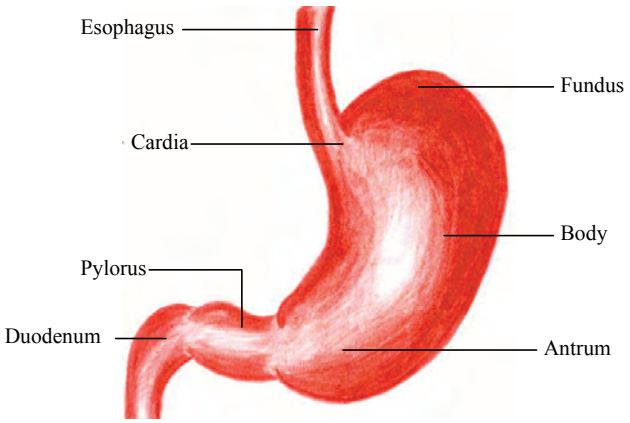

Figure 1. The esophagus and different parts of the stomach

2.2. Esophageal cancer

2.2.1. Classification: Two distinct histologic types of cancer occur in the esophagus, i.e. squamous cell carcinoma and adenocarcinoma. Adenocarcinoma of the esophagus may be misclassified as stomach cardia cancer and vice versa. It has been shown that there is some misclassification between esophageal and cardia adenocarcinoma in the Swedish Cancer Register. While the completeness of the register was 69-74% for cardia adenocarcinoma, there was a 16% underestimation in the incidence of esophageal adenocarcinoma.[15]

2.2.2. Descriptive epidemiology: Esophageal cancer ranks the eighth most common cancer worldwide and the sixth most common cause of death due to cancer.[1] There is enough epidemiological evidence indicating a dramatic increase in the incidence of esophageal adenocarcinoma in Western countries,[16-20] whereas a slight decrease has been noted for the incidence of esophageal squamous cell carcinoma, the dominant histologic type, in some reports,[16, 17] although not all.[18, 19] Furthermore, noticeable geographical variations exist for the rates of both histologic types of esophageal cancer.[21] Esophageal adenocarcinoma is a marked male predominant malignancy with a male to female ratio of 7-10:1, but the corresponding ratio for esophageal squamous cell carcinoma seems to be 3-4:1.

2.2.3. Risk factors

Tobacco and alcohol: Tobacco smoking and alcohol consumption have been known as the independent major contributing factors in the etiology of esophageal squamous cell carcinoma in Western population,[2] whereas they seem not to be strong risk factor for esophageal adenocarcinoma.[22-24] Both risk factors seem to be associated dose-dependently with esophageal squamous cell carcinoma risk and a successive decline in the risk occurs after cessation. However, the strong associations are not confirmed in all geographic areas, especially the very high risk areas.[25, 26]

Diet: A large number of epidemiological studies have investigated the association of different food items, vitamins or micronutrients with adenocarcinoma or squamous cell carcinoma of the esophagus. Most of these studies had a case-control design in which recall bias is a main concern and might bias the true association. However, although measurement error can lead to non-differential misclassification (and underestimation of effects) in studies with a prospective design, the results are more trustable and in some cases confirmed the findings from case-control studies. In general, the effect of dietary factors on two histologic types of esophageal cancer seems to be the same. The most consistent findings are protective effects of vegetables, fruits,[27, 28] vitamin C,[29-31] vitamin B2 (riboflavin),[2, 32] carotene,[29, 31, 33] vitamin B6 (pyridoxine),[31] vitamin E (tocopherol),[30, 33, 34] fiber,[31, 33, 35] folate,[31, 33] zinc,[33] and selenium,[36] whereas positive association has been reported between esophageal cancer risk and high intake of animal fat.[31, 35, 37] Data regarding vitamin A (retinol) are not consistent and both protective effect [33] and positive association[35] with this malignancy have been reported. While diets high in red and processed meat have been associated with esophageal cancer risk,[31, 38, 39] white meat and fish appear to be protective factors.[38, 40] Overall, it seems that 20-40% of esophageal cancer risk can be attributed to dietary factors.[27]

H. pylori: There are several relatively consistent reports of a strong inverse association between *H. pylori* seropositivity and risk of esophageal adenocarcinoma.[41-44] It has been suggested that the mechanisms underlying this obvious but enigmatic protection against esophageal adenocarcinoma can be *H. pylori*-induced atrophic gastritis, hypochlorhydria, and

reduction of acid reflux into the esophagus, which is a well-known and strong risk factor for esophageal adenocarcinoma, but studies specifically addressing the importance of severe gastric atrophy come up with conflicting results.[43, 45]

It was also reported that *H. pylori* infection may be associated with the risk of esophageal squamous cell carcinoma [43, 46] and the possible mechanism can be endogenous formation of N-nitroso compounds.[47, 48] Gastric corpus atrophy and hypoacidic situation result in overgrowth of microorganisms other than *H. pylori* which may favour formation of intragastric nitrosamines [49] – a suspected key risk factor for esophageal squamous cell carcinoma.[46] An association between N-nitroso compounds and gastrointestinal malignancies has been shown in animal models. [47, 50-52]

Gastroesophageal reflux: Gastroesophageal reflux disease is a common disorder in which the stomach's contents back up into the esophagus and may cause a wide range of esophageal damage. The most common symptomatic manifestation of this disease is heartburn. Gastroesophageal reflux disease is the most important and strongest risk factor for esophageal adenocarcinoma.[2] The magnitude of the excess risk is reported to be up to 40 and independent of other risk factors.[53] Barrett's esophagus, an intestinal-type columnar metaplasia in the epithelium of the lower esophagus, results mainly from gastroesophageal reflux and is associated with significant excess risk of esophageal adenocarcinoma.[2, 54] However, it is not clear whether Barrett's esophagus is a necessary precursor to all cases of esophageal adenocarcinoma.

Body weight: Body mass index (BMI) has been shown to be a strong risk factor for esophageal adenocarcinoma and the association is independent of other risk factors,[55] but the underlying biological mechanism is not clear. Conversely, some evidence shows an inverse association between BMI and esophageal squamous cell carcinoma.[2, 56] However, as weight loss occurs during early stage of this malignancy reverse causality can be a credible explanation.

Diagnosis, treatment and prognosis: The symptoms of esophageal cancer are usually dysphagia and weight loss. Upper endoscopic examination is necessary for all suspected patients and histopathologic examination of biopsy samples is used to establish the diagnosis. In the detection of metastases and staging of esophageal cancer, computed tomography (CT) scan and fluorodeoxyglucose positron emission tomography (FDG-PET) have been used. The only curative treatment is radical surgical removal of a localized cancer. Different methods have been used to restore continuity after esophagectomy in which the stomach or a part of intestine is used. Mechanical dilatation, self-expand stents, radiotherapy, and chemotherapy are the only options to improve passage in the majority, who are diagnosed in advanced stages, beyond any chance of cure. Esophageal cancer is one of the most lethal malignancies.[57] Five year survival rate is about 16% in the United States, 10% in Europe, and considerably lower in developing countries.[2]

2.3. Stomach cancer

2.3.1. Classification

More than 95% of all stomach neoplasms are adenocarcinoma, while other types such as gastric lymphoma, carcinoid and leiomyosarcoma are rare.[3] In this thesis we focused only on adenocarcinoma of the stomach. Esophagogastric junction adenocarcinomas (cardia cancer) are histologically identical to more distal adenocarcinomas but have different etiological

factors, and seem to be biologically more aggressive.[3, 57] The cardia – the most proximal part of the stomach – is a short segment of antrum-like mucosa, i.e. branched mucus secreting glands and absent of partial cells and chief cells. It seems that cardia-type mucosa may be enlarged due to proximal (gastroesophageal reflux cause columnar metaplasia of the squamous mucosa) or distal (*H. pylori* infection cause atrophy of the oxyntic glands) extension. Therefore, cardia mucosa may have three different origins – original cardia mucosa, distal esophageal squamous mucosa, and oxyntic mucosa immediately distal to the normal cardia – and it is conceivable that adenocarcinomas arising from this region have different etiologies.[58] However, it is not possible to distinguish the origin of the cancer by endoscopic or histological examination of the cancer. Moreover, there is a potential risk of misclassification of esophageal adenocarcinoma as cardia adenocarcinoma and vice versa. In a validation study for the Swedish Cancer Registry, a high quality registry, the completeness of cardia cancer registration was only 69-74% and the positive predictive value for cardia cancer was 82%.[5]

Based on Lauren's classification,[59] two histologic types of stomach adenocarcinoma exist, intestinal and diffuse. The former arises from precancerous lesions such as gastric atrophy, occurs more commonly in men than in women, is more frequent in older people, and represents the dominant histologic type in high risk areas. The latter is slightly more common in women and in younger patients.[57] The change in the incidence of both subtypes seems to be the same and also both intestinal and diffuse types of distal stomach adenocarcinoma are associated with *H. pylori* infection.[3]

2.3.2. Descriptive epidemiology

Adenocarcinoma of the stomach is the second leading cause of death due to cancer worldwide.[1] With an estimated 934,000 new cases per year, stomach cancer is the fourth most

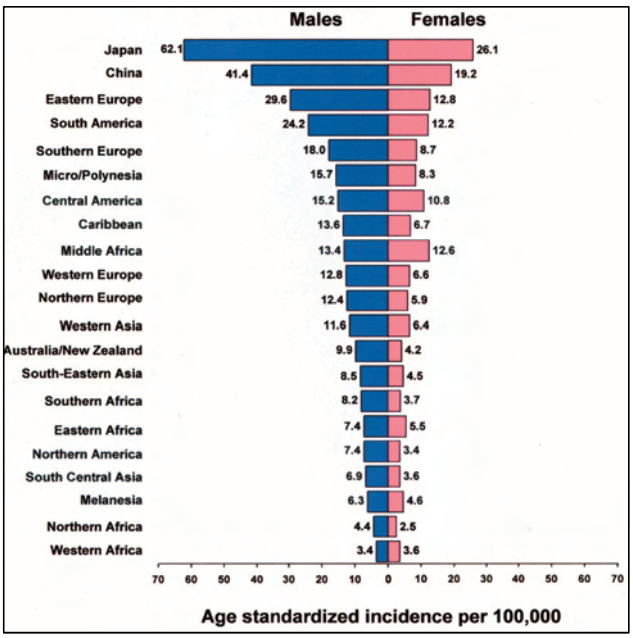

Figure 2. Age-standardized Incidence Rates for Stomach Cancer. Reprinted from *Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74-108.* with permission from the publisher

common cancer globally. This malignancy occurs more in developing countries and almost two-thirds of the cases are reported in these populations. Male to female ratio is about two in most geographic areas (Figure 2) and it is rarely seen in individuals younger than 50 years. There is a wide variation in the geographical distribution of this cancer. In men, the age standardized incidence rates (ASR) in high risk areas including East Asia, Eastern Europe, and parts of Central and South America are > 20 per 100,000 person-years, while in low risk areas such as Southern Asia, North and East Africa, North America, and Australia, standarized incidence rates are < 10 per 100,000 person-years.

It seems that the remarkable spontaneous global decline in the incidence of stomach cancer is confined solely to the non-cardia stomach adenocarcinoma.[60]

2.3.3. Risk factors

Etiology of stomach cancer, like most other malignancies, seems to be multifactorial.

***H. pylori* infection**: The presence of spiral-shaped organisms in biopsies of the mammalian stomach has been reported first by Bizzozero (1893).[61] However, these spiral bacteria were not successfully isolated until 1983, and since then the association between *H. pylori* infection and gastric ulcers was established.[62] After careful evaluation of the evidence, *H. pylori* was also designated as a class I gastric carcinogen by the International Agency for Research on Cancer (IARC) in 1994.[63]

H. pylori is the only organism that can survive in the highly acidic stomach using urease to convert urea to carbon-dioxide and ammonia by which it neutralizes its surrounding environment.

The prevalence of *H. pylori* infection is higher among low socioeconomic class and families with crowded living conditions.[64] The geographic distribution of *H. pylori* tends to follow this trend. The prevalence of *H. pylori* infection among individuals over 40 years of age is more than 60% in most developing countries,[65-68] some economically developed countries [69-71] and African Americans.[72] However, in Caucasian Americans [72] and most developed countries,[73, 74] including Sweden,[75] the prevalence in the mentioned age group is about 40%.

It seems that *H. pylori* infection is the strongest and most important known risk factor for non-cardia stomach cancer. Epidemiological studies with a careful design to minimize misclassification of exposure (*H. pylori* infection) reported a relative risk of 20 or more for non-cardia stomach cancer.[76-78] Due to small number of cases and diversity of anatomic subsite definitions, the available data for association of cardia cancer with *H. pylori* infection is not consistent. It has been suggested that cardia cancer can be divided to two subtypes with different etiologic factors, i.e. type A being a consequence of atrophic gastritis associated with *H. pylori* infection and type B being a consequence of short-segment gastroesophageal reflux disease.[58]

It seems that highly specific interactions between *H. pylori* adhesions and host receptors are responsible for exact tropism that may cause different pathological outcomes.[79] Cytotoxin associated gene A (*cag A*) is part of a 40 kb gene segment, the *cag* pathogenicity island, and is considered a virulence marker. About 60-70% of strains in Western societies and more than 90% of strains in Asian population carry this gene. This means that the presence or absence of *cagA* alone is not enough to distinguish between virulent and nonvirulent *H. pylori* isolates.

H. pylori strains that induce higher levels of CagA phosphorylation in epithelial cells induce more cytoskeletal changes, and are more likely to be associated with stomach cancer. Another gene is *vacA* with reported mutations in the signal sequence segment (s) and in the intermediate segment (m).[80] This gene-encoded protein has vacuolating activity and degeneration of epithelial cells in some strains whereas others do not cause vacuolation. *H. pylori* strains that have an in-frame or functional copy of *oip*A are reported to more likely cause duodenal ulcer disease, more bacterial colonization, severe gastric inflammation and increased level of IL-8.[79] Furthermore host immune response has an important role in the pathological outcome. Some outer membrane proteins in *H. pylori* such as BabA, SabA, HopA and OipA are reported to have special host receptors and are critical for adhesion which is required for prolonged inhabitance of the stomach. It is plausible that host genetic variations may influence or decide outcomes, like gastroduodenal ulcers or stomach cancer, after *H. pylori* infection.[81-85]

The real mechanism(s) by which *H. pylori* can increase the risk of stomach cancer is not clear yet. There are some suggestive mechanisms and most probably a combination of them may be behind the putative carcinogenic effect of *H. pylori*. Chronic inflammation induced by *H. pylori* might cause epithelial DNA damage via various pathways such as boosted cell turnover, increased oxidative stress, and distorted proliferation-apoptosis balance.[86-88] Infection by *H. pylori* results in reduction in ascorbic acid level in the stomach [89, 90] which can increase stomach cancer risk. In a normal stomach ascorbic acid can decrease cancer risk by scavenging for potentially mutagenic free radicals and nitrites, and controlling cell differentiation. Another consequence of *H. pylori* infection is enhanced cell proliferation that increases the number of cells in S-phase which are sensitive to mutagens. *H. pylori* infection also induces release of some mutagenic substances by increasing expression of inducible nitric oxide synthase (iNOS) [91, 92] and cyclooxygenase-2 (Cox-2).[93]

Immigration studies show that when people move from a high risk area for stomach cancer to a low risk area their risk remains stable but the risk in next generation changes towards the level of local population. It seems that early life exposures – possibly *H. pylori* – are important for the future risk of stomach cancer.[94, 95] However, with such a high prevalence of *H. pylori* infection in all regions, it is clear that the factors other than *H. pylori* infection are also of importance.

Diet: Because the stomach acts as a reservoir and all ingested items can potentially change intragastric environment, a considerable number of etiologic studies have tried to explore the role of diet in the stomach cancer development. It has been shown that a diet rich in fresh fruits and vegetables is associated with a significant reduction of stomach cancer risk [3, 28, 96, 97] with a risk reduction of about 50% among individuals with a high consumption of these plant foods compared to those with the lowest consumption.[3, 98, 99] Among different components of fruits and vegetables associated with stomach cancer risk, antioxidants tend to have the strongest protective effect.[3, 28, 30, 96, 100, 101] The mechanism by which antioxidants can protect against stomach cancer is yet to be established, but it has been suggested that these substances may have a free radical scavenging role in the stomach,[102] and/or inhibit formation of N-nitroso compounds.[103] Vitamin C, as an important antioxidant, seems to inhibit the growth of *H. pylori* in the human stomach.[104] Vitamin C concentration in gastric juice is lower in the presence of gastric pathologic lesions [105] and a low blood level of vitamin C and high concentration of nitrite in the gastric juice of stomach cancer patients is reported.[106] More credible data come from randomized controlled trials [101, 107] in which vitamin C supplementation could increase the regression rate of gastric precancerous lesions or slow the

progression of gastric mucosal atrophy. Moreover, dietary fibers have been shown to have a protective effect against stomach cancer.[31, 33, 35, 108] On the other hand, high intake of salt and salty foods is associated with an increased risk of stomach cancer, possibly due to induced superficial and atrophic gastritis.[109, 110]

Three common problems in nutritional epidemiology are measurement error in dietary intake, recall bias – in the case-control design – and limited number of food items in food frequency questionnaires. Moreover, a small effect of a particular nutrient or food item is difficult to find and also looking for the effects of a large number of nutrients or food items increases the probability of chance finding, which may explain inconsistencies in studies of association between diet and cancer risk. In fact, people who differ in consumption of one important nutrient or individual food tend to differ in main consumption of other important nutrients or foods. Thus, the attribution of an increased or decreased risk of cancer to one particular nutrient or food may sometimes be inappropriate, as strong correlations between items prohibit the full disentanglement. Prospective design with stringent criteria for exposure measurements and controlling for possible confounders could be helpful. Also focusing on dietary patterns can help to find the role of overall diet in cancer etiology as a complementary approach to more traditional analysis of nutrients or foods. Furthermore, it can provide a dietary guideline which has important public health implications.

N-nitroso compounds: Endogenous or exogenous nitrosamines have been suspected as the carcinogenic factor especially for the stomach,[31, 111, 112] while vitamin C may inhibit this effect.[103, 113] Although results of cohort studies are inconsistent, evidence from case-control studies supports a positive association between these carcinogenic compounds and stomach cancer.[114] As mentioned above, a main concern in these studies would be exposure measurement which could prohibit finding the true associations. The situation is more problematic as it seems that endogenous N-nitroso compounds could be formed in a much higher range than exogenous ones.[115]

Reflux and obesity: Gastroesophageal reflux is a well-established and important risk factor for stomach cardia cancer.[53, 116] The chronic reflux of gastric juice, consisting of hydrochloric acid, pepsin and bile seems to damage the gastroesophageal junction and esophageal squamous mucosa progressively.[117] Data on the association of body mass index and stomach cardia cancer is not homogenous. In a recent meta-analysis a high body mass index was associated with a 50% excess risk of cardia cancer.[55]

Tobacco smoking: Tobacco smoking is associated with both anatomic subtypes of stomach cancer and an about 60% increased risk, particularly among men, is reported.[3] It seems that the association is stronger among individuals with low dietary intake of fruit and vegetables.[118]

Medical interventions: Since intragastric environment changes significantly in vagotomized patients and those who have undergone partial gastric resection, studies of stomach cancer risk among these patients have attracted considerable attention. Numerous studies in the past have addressed stomach cancer risk among patients who have undergone partial gastric resection for peptic ulcer, but the results have not been consistent.[119, 120] In fact, the results range from a more than two-fold increased to an 80% decreased risk.[119] Increased risks for stomach cancer among patients who underwent vagotomy for peptic ulcer have been reported in some studies.[121-123] Almost all of the previous studies have compared operated patients to the general population and did not consider the risk associated with the underlying disease,

and/or follow-up time was relatively short. Another medical intervention is cyclooxygenase (COX) inhibitors such as aspirin or some other non-steroidal anti-inflammatory drugs (NSAIDs) which seem to protect against stomach cancer.[124]

Female hormones: The reasons for the almost universal male predominance in stomach cancer incidence remain unclear. The prevalence of known risk factors for stomach cancer, such as for example *H. pylori* infection and tobacco smoking, does not seem to entirely explain this enigmatic difference.[3] A male preponderance was also reported in a rat experimental model of stomach cancer [125] and there was evidence that female hormones might have a protective effect against stomach cancer development in rats.[126] Furthermore, it has been reported that functional estrogen receptors alpha [127, 128] and beta [129, 130] exist in human stomach mucosa. Therefore, it has been hypothesized that sex hormones – notably estrogens – protect women against stomach cancer.[131] A possible mechanism for the role of estrogen on stomach cancer risk is up-regulation of *TFF1* gene by estrogen.[132] TFF proteins are secreted-type proteins with trefoil domain existing in the mucous layer of the gastrointestinal tract, with a key role in stabilizing and repairing mucosal layer particularly after injury.[132]

Pregnancy has been suggested as a natural model to test the role of sex hormones on stomach cancer development. Pregnant women have a unique endocrine milieu in which serum levels of some hormones including estrogens are markedly elevated during the course of gestation.[133] The hyper-estrogenic state during human pregnancy increases continually as the pregnancy progresses, and the amount of estrogen produced each day during the last few weeks of pregnancy is more than 1000 times higher than that in non-pregnant women. Few epidemiological studies have investigated the association between reproductive factors or exogenous female hormones and stomach cancer risk, and the results have been inconsistent [134-141] (Table 1).

Table 1. Summary of previous studies on the association between reproductive factors and stomach cancer risk

	Study population	Exposure (reference group)	Estimate of relative risk for stomach cancer
A: Endogenous hormone			
Frise S, et al.[137] 2006 (case-control study in Canada)	326 cases, 326 controls	> 3 pregnancies (nulliparity)	Overall 0.56 (0.32-0.99) Cardia 0.51 (0.18-1.43) Noncardia 0.71 (0.37-1.36)
		Age ≤24 at first pregnancy (nulliparity)	Overall 0.55 (0.31-0.96) Cardia 0.69 (0.27-1.77) Noncardia 0.71 (0.38-1.32)
		Age ≥25 at first pregnancy (nulliparity)	Overall 0.67 (0.38-1.18) Cardia 0.47 (0.17-1.30) Noncardia 0.83 (0.44-1.57)
		Years of fertility ≥39 (≤27 years)	Overall 0.80 (0.49-1.31) Cardia 0.90 (0.37-2.19) Noncardia 1.03 (0.57-1.88)
		Post-menopause (pre-menopause)	Overall 1.99 (0.98-4.05) Cardia 4.80 (1.09-21.1) Noncardia 1.77 (0.76-4.11)
Kaneko S, et al.[141] 2003 (cohort study in Japan)	40,535 women, 156 cases	Ever pregnant (never) > 3 pregnancy (nulliparity) Age ≥24 at first pregnancy (≤22 yr) Years of fertility ≥36 (≤30 years)	0.62 (0.27-1.41) 0.60 (0.29-1.28) 1.07 (0.70-1.63) 0.83 (0.37-1.54)
Inoue M, et al.[134] 2002 (case-control study in Japan)	365 cases, 1825 controls	Ever pregnant (never) Risk per child Age≥27 at first pregnancy (≤23) Years of fertility ≤32 (≥39 years)	1.13 (0.75-1.70) 1.02 (0.93-1.12) 0.71 (0.47-1.08) 1.25 (0.86-1.83)
Palli D, et al.[135] 1994 (case-control study in Italy)	339 cases, 515 controls	Ever pregnant (never) > 3 pregnancies (1 pregnancy) Age ≥20 at first pregnancy (≤31) Years of fertility ≥40 (≤32years)	1.0 (0.6-1.5) 1.2 (0.7-2.1) 0.9 (05-1.5) 0.6 (0.4-0.9)
La Vecchia C, et al. [136] 1994 (case-control study in Italy)	229 cases, 614 controls	> 3 pregnancies (nulliparity) Age ≤20 at first pregnancy (≥30) Years of fertility ≥39 (≤31years)	1.9 (1.0-3.5) 2.3 (1.0-5.6) 0.7 (0.4-1.1)
Kvåle G, et al.[138] 1994 (cohort study in Norway)	61,774 women, 492 cases	> 4 pregnancies among women under 50 years old (nulliparity) > 4 pregnancies among women over 50 years old (nulliparity)	1.12 (p for trend = 0.71) 0.99 (p for trend = 0.98)
Plesko I, et al.[139] 1985 (case-control study in Slovakia)	3,613 cases, 182,415 controls	> 5 pregnancies (nulliparity) > 5 pregnancies (one pregnancy)	1.34 (p for trend <0.001) 1.21 (p for trend <0.01)
Miller AB, et al.[140] 1980 (case-control study in Canada)	260 stomach cancer	> 3 pregnancies (nulliparity)	1.59 (p for trend =0.05)

B: Exogenous female hormones

	Study population	Exposure (reference group)	Estimate of relative risk for stomach cancer
Lindblad M, et al. [142] 2006 (case-control study in the United Kingdom)	313 cases, 3191 controls	Hormone replacement therapy	Overall 0.48 (0.29-0.79) Cardia 0.68 (0.23-2.01) Noncardia 0.34 (0.14-0.78)
Chandanos E, et al.[143] 2006 (cohort study in Sweden)	138,885 women with breast cancer, 21 cardia and 341 non-cardia cancer cases	Unexposed to tamoxifen (general population) 1970-1987	Cardia 0.75 (0.42-1.32) Noncardia 1.47 (1.30-1.66)
		Exposed to tamoxifen (general population) 1988-2003	Cardia 0.96 (0.5-1.86) Noncardia 1.27 (1.03-1.57)
Lindblad M, et al.[144] 2004 (cohort study in Sweden)	148,238 men with prostate cancer, 71 cardia and 415 non-cardia cancer cases	Exposed to estrogen (general population) 1970- 1980	Overall 0.87 (0.78-0.98) Cardia 0.70 (0.37-1.20) Noncardia 0.86 (0.74-1.01)
		Unexposed to estrogen (general population) 1981-2000	Overall 0.99 (0.89-1.11) Cardia 1.14 (0.87-1.48) Noncardia 0.96 (0.85-1.09)
La Vecchia C, et al. [136] 1994 (case-control study in Italy)	229 cases, 614 controls	Ever oral contraceptive use (never)	1.28 (0.5-3.5)
		Ever estrogen replacement therapy use (never)	0.54 (0.3-1.1)
Frise S, et al.[137] 2006 (case-control study in Canada)	326 cases, 326 controls	Ever oral contraceptive use (never)	Overall 0.79 (0.43-1.45) Cardia 0.78 (0.25-2.48) Noncardia 0.66 (0.33-1.33)
		Ever estrogen replacement therapy use (never)	Overall 0.72 (0.37-1.40) Cardia 0.37 (0.08-1.71) Noncardia 0.94 (0.46-1,95)
Kaneko S, et al.[141] 2003 (cohort study in Japan)	40,535 women, 156 cases	Ever estrogen replacement therapy use (never)	0.60 (0.19-1.88)

Genetic susceptibility: Clearly, stomach cancer only occurs in a minority of patients infected with *H. pylori*. Some epidemiological studies reported influence of genetic factors on susceptibility of stomach cancer. In a relatively big twin-pair study [145] monozygotic and dizygotic twins with a case partner had 10-fold and 6.6-fold higher stomach cancer risk, respectively, compared to twins whose partner did not have stomach cancer. Stomach cancer risk has been associated with polymorphisms in genes involved in inflammatory response,[83, 84, 146-151] mucosal protection,[152, 153] metabolic enzymes, oxidative damage,[154-160] DNA damage and oncogenes.[161-164] Moreover, a number of familial stomach cancer syndromes have been defined in about 10% of the cases, which based on the histopathology of the tumors, number of documented cases in the family and age of onset, can be categorized into four different groups: hereditary diffuse stomach cancer,[165] familial diffuse stomach cancer, familial intestinal stomach cancer [166] and familial stomach cancer.

2.3.4. Diagnosis, treatment and prognosis:

Symptoms of stomach cancer are nonspecific, therefore most patients are diagnosed with advanced stage cancer. Gastroscopic examination is considered the best method to diagnose stomach cancer. This procedure also allows biopsy for a definite histopathologic diagnosis. Computed tomography imaging, positron emission tomography, ultrasound, and other modern techniques have sometimes been used for the staging evaluation and more detailed information. Curative radical surgical removal of a localized stomach cancer – partial or total gastrectomy – is the choice of treatment for non-advanced tumors. Chemotherapy or radiotherapy may be used in treatment of tumors with advanced stages.[57] The prognosis of stomach cancer is generally poor. However, mass screening in Japan and early diagnosis due to higher number of endoscopic examinations for GI disorders in North America resulted in a relatively better survival for this malignancy.[1]

2.4. Peptic ulcer

Generally, a peptic ulcer has been defined as a mucosal defect with a diameter of 3-5 mm or greater in the stomach and/or duodenum due to active inflammation. Prevalence of peptic ulcer diseases has been reported to be about 4% in general Western populations during last 20 years.[167-169] Lifetime prevalence of peptic ulcer disease is reported to be about 10% in the United States.[170] Duodenal ulcers and gastric ulcers have some common characteristics regarding pathogenesis, symptoms, diagnosis, and treatment; however, these disorders have several dissimilarities. The pathophysiology of peptic ulcer disease has been connected to an imbalance between aggressive factors such as gastric hypersecretion and inflammatory cells, and protective factors, for instance prostaglandin and bicarbonate in the stomach and duodenum.[13] About 70-90% of all duodenal ulcer patients [171-177] and about 70% of gastric ulcer patients [178, 179] are *H. pylori* positive. An interaction between *H. pylori*, host factors and environmental factors may determine pattern of gastritis and hence clinical outcome. Some environmental factors such as tobacco smoking and consumption of salty foods are associated with low acid secretion status in which *H. pylori* may colonize the corpus with intense inflammation and consequently further reduce acid secretion.[180] In contrast, patients with high gastric acid output experience antral predominant gastritis which is associated with hypergastrinemia and increased acid secretion. In this group of infected patients duodenal ulcer might occur due to increase in duodenal acid load, *H. pylori* colonization of gastric metaplasia, and loss of duodenal mucosal defense [14]

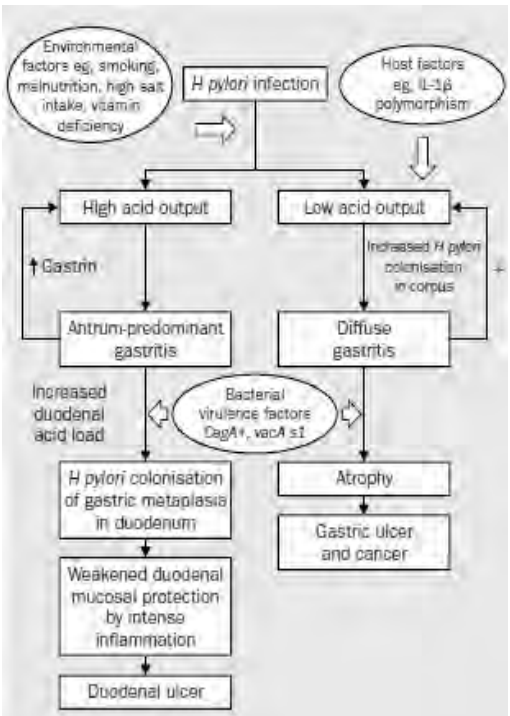

Figure 3. The relationship between host, environment, and *H pylori* infection in the development of gastric and duodenal ulcers
"Reprinted from The Lancet, Volume 360, Francis KL Chan and WK Leung, Peptic-ulcer disease, Page 9, Copyright (2002), with permission from Elsevier."

(Figure 3). It seems that the host immune response also plays an important role in the different pathological outcomes after *H. pylori* infection.[84, 181]

Some peptic ulcers have been attributed to the non-steroidal anti-inflammatory drugs (NSAIDs).[182-184] The NSAIDs can damage the stomach by different mechanisms such as suppressing prostaglandin synthesis, topical injury, and changing the action of surface-active phospholipids which causes reduction in the hydrophobicity of the mucus gel layer. The NSAIDs inhibit cyclooxygenase which synthesizes prostaglandins. It has been shown that two different isoforms of this enzyme exist, i.e. COX-1 and COX-2.[185] The former is involved in the maintenance of tissue integrity and homeostasis, whereas COX-2 is involved in inflammatory responses. Traditional NSAIDs have both the therapeutic effects (inhibition of COX-2) and side effects (inhibition of COX-1). This knowledge has led to the development of highly selective COX-2 inhibitors. Clinical benefits of these drugs compared to traditional NSAIDs, such as fewer ulcers and related complications, have been confirmed in several studies.[186-188]

Possible interaction between *H. pylori* and NSAIDs in association with the risk of peptic ulcer diseases have been the focus of several studies in the last years, but the results are inconsistent. However, there is evidence supporting that *H. pylori* is a risk factor for NSAIDs-related peptic ulcers [189] and increases the possibility of complications, e.g. bleeding.[190] Moreover, it has been shown that eradication of *H. pylori* can decrease the risk of peptic ulcer in NSAID users,[191, 192] although conflicting results exist.[193] *H. pylori* and NSAIDs are responsible for about 90% of peptic ulcers.[13]

Recently an increase in the proportion of ulcers which are associated neither with *H. pylori* nor with NSAIDs, so called non-NSAID non-*H. pylori* ulcers, was reported in some studies.[167, 173, 194, 195] It is conceivable that the decline in prevalence of *H. pylori* infection particularly in developed countries has led to this changing pattern of peptic ulcer disease.

The most common complication of peptic ulcer diseases is bleeding that occurs in about fifteen percent of patients. Perforation is the second most common complication of this disorder and occurs in about seven percent of patients. These complications seem to be more common among elderly subjects and might be associated with NSAIDs use. Other complication is gastric outlet obstruction.[170]

Common symptoms of peptic ulcer diseases are epigastric pain described as a burning and nocturnal pain. In duodenal ulcer pain usually occurs 90 minutes or more after a meal and can wake the patient from sleep after midnight and relieved by food or antacids. The typical pain in gastric ulcer patients, however, starts just after a meal and weight loss may happen due to reduced appetite caused by fear of pain. As no specific symptom helps for diagnostic evaluation of peptic ulcer disease a radiographic (barium study) or an endoscopic procedure is needed.

Before the development of effective pharmacologic suppression of gastric acid secretion in the 1970s, surgical treatment – partial gastric resection or vagotomy – was the mainstay in the management of this disorder in most cases but the introduction of H2-receptor antagonists and later proton-pomp inhibitors resulted in a dramatic decline in the elective surgical treatments.[196] Discovery of *H. pylori* and its association with peptic ulcer diseases by Marshal and Warren [62] further changed the management of these ulcers.

2.4.1. Gastric ulcer

Gastric ulcer patients tend to be older than duodenal ulcer patients. It has been well known that the patterns of gastritis differ in gastric ulcers and duodenal ulcers.[197] Gastric ulcer is associated with a corpus-predominant or even diffuse gastritis, while antrum-predominant gastritis is the characteristic of duodenal ulcer.[14] Corpus-predominant gastritis is connected to low acid output, gastric atrophy, and stomach cancer. It seems that the distribution of *H. pylori* colonization is linked to gastric acid secretion. Studies on *H. pylori* infected individuals have shown that acid-suppressing treatment can change the pattern of intragastric infection from antral-predominant to fundus-predominant,[198-200] however, this change seems to be reversible in most cases after termination of treatment.[200] Environmental and host factors also play an important role in the distribution of *H. pylori* in the stomach, and consequently the long term outcome of infection. Low socioeconomic status principally during childhood in which malnutrition and infections are common might be a key factor in the enigma of the stomach response to *H. pylori* infection.[180] It has been well known that gastric ulcer is associated with an excess risk of stomach cancer.[201]

2.4.2. Duodenal ulcer

The incidence of duodenal ulcer and its complications declined due to eradication of *H. pylori* infections after the discovery of this organism.[170]

In spite of enough available evidence to support the key role of *H. pylori* in the pathogenesis of duodenal ulcer, the underlying mechanism is not yet clear. However, it is well known that duodenal ulcer patients have increased basal and stimulated acid output, and reduced inhibitory effect of somatostatin on gastrin release,[202] although there is a substantial overlap in the level of gastric acid secretion between these patients and controls. Moreover, an over secretion of acid has been reported in the case of antrum-predominant *H. pylori* gastritis, regardless of duodenal ulcer.[203] Some research suggests that gastric metaplasia of the duodenum – results from increased duodenal acid load – might be essential for the development of duodenal ulcer.[204] It seems that *H. pylori* colonize the areas with gastric metaplasia in the duodenal bulb [205] and this infection may be one of the critical steps in the development of ulcers. However, there is conflicting result in which no significant difference was reported in the prevalence of gastric metaplasia between patients with duodenal ulcer and the control group.[206] But a defect in bicarbonate secretion in the proximal duodenum in response to acidification of the duodenum exists only in duodenal ulcer patients.[206]

Although approximately 90% of duodenal ulcer patients are seropositive for *H. pylori* and a strong overall association between *H. pylori* seropositivity and non-cardia stomach cancer risk is well established,[27, 76, 78, 207] unexpectedly, these ulcer patients have a lower risk of stomach cancer.

3. Aims

The aims of this thesis were:

- To study the association of dietary patterns and the development of cancers from the esophagus or gastroesophageal junction.

- To evaluate the risk of esophageal cancer by histology among patients hospitalized for gastric ulcer or duodenal ulcer.

- To estimate the risk of cardia and non-cardia stomach cancer among unoperated patients hospitalized for gastric ulcer or duodenal ulcer. Also to study stomach cancer risk among vagotomized patients and those who underwent partial gastric resection while taking the disparate baseline risks into consideration.

- To study the association between parity and the risk of cardia and non-cardia stomach cancer.

4. Material and Methods

4.1. Ethical considerations

For study I informed consent, both written and oral, was obtained from each subject before the interview, and the study was approved by all regional ethics committees in Sweden. Studies II, III and IV were approved by the Regional Ethics Committee of Karolinska Institutet.

4.2. Study I

4.2.1. Study Design

The Swedish Esophageal and Cardia Cancer Study (SECC) is a nationwide case-control study from December 1994 to December 1997 that encompassed the whole population of Sweden younger than 80 years and born in Sweden. All incident cases of adenocarcinoma of the esophagus or stomach cardia and half of the newly diagnosed cases of esophageal squamous cell carcinoma – born on even-numbered days – were eligible for inclusion. A comprehensive organization for the rapid ascertainment of cases, involving a responsible person in every department of general surgery, thoracic surgery, otorhinolaryngology, oncology, and pathology in Sweden, as well as continuous collaboration with all the regional tumor registries, ensured that every potential case patient throughout the country was identified soon after diagnosis. The control subjects were selected randomly from among the Swedish population and frequency matched to resemble the age (within 10 years) and sex distribution among the esophageal adenocarcinoma cases, through the use of the Total Population Register, which is computerized and updated continuously.

Uniform routines for the documentation of the tumors were introduced at all participating sites to reduce misclassification of the tumor site or histologic type. The distances between the gastroesophageal junction and the upper and lower borders of the tumor were measured during endoscopy. In 22 patients it was impossible to pass the endoscope beyond obstructing tumors after dilatation or the gastroesophageal junction could not be identified, therefore the borders of the tumor were measured as distances to the incisor teeth, and endoscopy was supplemented with radiological imaging. Serial biopsy specimens were obtained every 2 cm from the proximal stomach, the gastroesophageal junction, the esophagus until normal squamous cell epithelium was reached as well as proximal, distal, and lateral to the tumor. Biopsy samples, surgical specimens, or both were reviewed by a single pathologist and in the case of uncertainty all available information was reviewed by a panel of investigators to classify the case. For a case to be classified as a cancer of the stomach cardia, the center of tumor should be within 2 cm proximal, or 3 cm distal, to the gastroesophageal junction. Columnar-cell metaplasia of the specialized type, with goblet cells and villiform surface configuration of the mucosa resembling the features of the intestines was defined as Barrett's esophagus. Five patients with junctional or fundus metaplasia recorded more than 3 cm proximal to the gastroesophageal junction were also classified as having Barrett's esophagus. In seven patients in whom Barrett's esophagus was detected adjacent to an adenocarcinoma located in the stomach cardia, the tumors were classified as esophageal. Squamous cell carcinomas were classified as esophageal even if the location was the stomach cardia.

4.2.2. Dietary assessment and demographic characteristics

It was impossible to blind the interviewers to the case or control status of the subjects, but they were unaware of the study hypotheses and were trained to treat the case patients and controls strictly the same. A modified version of a previously evaluated food frequency questionnaire, including 63 food and beverage items of interest,[208] was used to evaluate dietary habits of the controls and cases 20 years before the interview. The usual frequency of consumption of each food item was asked and answers were in terms of number of times per day, week, month or year. We transformed the data into average monthly intake for every food item, by assuming 1 month equal to 4 weeks or 30 days. To reduce the complexity of data we grouped the individual items into 26 separate food groups. Grouping was based on the similarity of nutrient profiles or their association with cancer, and is similar to what has been used in previous Swedish studies.[209-211] The questions also covered demographic characteristics, living conditions during childhood and adolescence, gastroesophageal reflux symptoms, anthropometric measures, smoking, history of medication use and occupational history.

In total, 189 (88%) patients with esophageal adenocarcinoma, 167 (73%) of those with esophageal squamous cell carcinoma, 262 (84%) of those with stomach cardia adenocarcinoma, and 820 (73%) of population controls underwent computer aided face-to-face interviews by specially trained professional interviewers from Statistics Sweden. Main reasons for nonparticipation among cancer patients were poor clinical condition or death shortly after diagnosis, while that for controls was unwillingness. We excluded eight subjects from the analysis because their log scale of total energy intake were below or above three standard deviations from the mean, indicating errors in their responses to the dietary questions. We further excluded four subjects due to missing body mass index, and another three subjects due to poor responses regarding dietary questions. Finally 185 cases with esophageal adenocarcinoma, 165 with esophageal squamous-cell carcinoma, 258 with stomach cardia adenocarcinoma, and 815 controls remained for analysis.

4.2.3. Statistical analyses

Principal components method for factor analysis in SAS (version 8.2; SAS Institute, Cary, North Carolina) was used to identify potential dietary patterns among population controls only. Using the correlation matrix of the 26 food groups, orthogonal varimax rotation method was applied to achieve simpler structure facilitating interpretation. Although factors with eigenvalues (a measure of the amount of variance that is accounted for) greater than 1.0 indicate that the factor describes more of the variability in the data than the average variable for any individual item within the factor, selection of factors was based on interpretability and Scree plot.[212] In fact, Scree plot showed a clear break and also increasing the number of extracted factors did not materially change three previously extracted factors. Eventually we selected all three factors with eigenvalues greater than 1.5. Factor loading is correlation coefficients between food groups and dietary patterns and positive loading in a factor indicates a direct association with the factor, while negative loading indicates that the food group is inversely associated with the factor. We then calculated for each study subject factor scores for these three dietary patterns. Factor scores were divided into tertiles according to the distribution in controls. We used Chi square test to check the differences of distribution of categorical variables (e.g., symptomatic gastroesophageal reflux and smoking), and ANOVA test to check differences of distribution of continuous variables (e.g., body mass index) across dietary pattern score categories.

Unconditional logistic regression was used to estimate odds ratios (ORs) with 95% confidence intervals (CIs). Age, sex, years of education, symptomatic gastroesophageal reflux, body mass index, smoking, physical activity, and total energy intake were considered as potential confounders and were also included in the models. Because smoking is a well known risk factor for esophageal cancer we used pack-years of smoking as a categorical variable in the model. As a basis for the linear trend tests across categories of dietary pattern scores, each subject was assigned the median value of the specific category, and this variable was treated as a continuous variable in modeling. All p values reported are two-sided.

4.3. Study II

Study II was based on the data from the Swedish Inpatient and Cancer Registers.

The Swedish Inpatient Register

The Swedish Inpatient Register includes data on individual hospitalizations that have been collected by the National Board of Health and Welfare, a government agency under the Ministry of Health and Social Affairs, since 1964. The coverage of this register was 60%, 85% and 100% of the Swedish population in years 1969, 1983 and 1987, respectively. Each record contains the National Registration Number (NRN), an individually unique personal identifier assigned to every Swedish resident from birth or immigration, as well as medical data, including diagnoses at discharge (coded according to the *International Classification of Diseases,* 7th Revision [ICD-7] [213] through 1968, 8th revision [ICD-8] during 1969-1986, 9th revision during 1987-1996, and 10th revision thereafter) and surgical procedures (coded according to the Swedish Classification of Operations and Major Procedures through 1996 and the Nordic medico-statistical committee (NOMESCO) classification of surgical procedures thereafter).

The Swedish Cancer Register

The national Swedish Cancer Register, established in 1958, contains individual data on all newly diagnosed malignant tumors in Sweden, and is more than 98% complete.[5, 214] All the health care providers in Sweden are obliged to report newly detected cancer cases to the registry. There are six regional registries in Sweden that perform the registration, coding, major check-up and correction of the records. The regional registries annually send the data of newly registered cases to the National Cancer Register. The Cancer Register used ICD-7 as the coding scheme from the beginning, and a WHO pathology code was also used to record histological types of cancer where applicable.

4.3.1. The study population

All patients in the Inpatient Register who survived to be discharged between 1965 and 2003 with a diagnosis of duodenal ulcer (ICD-7 code 541, ICD-8 and ICD-9 code 532, and ICD-10 code K26) or gastric ulcer (ICD-7 code 540, ICD-8 and ICD-9 code 531, and ICD-10 code K25) were considered for inclusion in the cohorts. We did not include individuals with records of both gastric ulcer and duodenal ulcer. For each potential subject, we identified the first recorded hospitalization for the ulcer as the index episode.

To check the validity of the records for each potentially eligible subject the NRNs were checked in the nationwide registers of Total Population, Emigration and Causes of Death and

NRNs that could not be located in any of these registers were regarded invalid. In total, 6,643 records were excluded for this reason and because of other inconsistencies. We further excluded 22,946 patients with diagnosis of any cancer before or at the time of the index episode, and 12,323 individuals who died during the index hospitalization. Finally, our cohorts encompassed 181,053 individuals.

4.3.2. Follow-up

We got censor information by linking the NRNs to the nationwide and essentially complete registers of Migration and Causes of Death. We used the national Swedish Cancer Register to identify incident cancer cases in the cohort. We only considered first cancers and excluded all benign tumors and cancers found incidentally at autopsy. We used ICD-7 code of 150 for esophageal cancer, while the pathology code '146' and '096' denoted squamous cell carcinoma and adenocarcinoma, respectively. The start point of our study was 1965 and the patients in the cohort were followed from the date of discharge from their first recorded in-hospital episode with duodenal ulcer or gastric ulcer until the date of a diagnosis of any cancer, emigration, death, partial or total gastrectomy, vagotomy, or until December 31, 2003, whichever occurred first.

We were concerned about a selection bias that may happen due to prodromal symptoms from yet undetected preclinical esophageal cancers by which the probability of being hospitalized with a peptic ulcer diagnosis increases. Therefore, we excluded the data related to the first year of follow-up from our analysis to eliminate such selection bias. On the other hand, since most hospitalized patients with peptic ulcer will undergo an upper endoscopy, it is expected that the population is newly screened at time of entry, and that the incidence of esophageal cancer will be artificially decreased during the first years of follow-up.

4.3.3. Statistical analysis

We calculated the standardized incidence ratio (SIR), the ratio of the observed to the expected number of cancers, as a measure of relative risk for esophageal cancer among duodenal and gastric ulcer patients. The calculation of the expected number of cancers was based on the person-time experienced by the cohort members, divided into strata of sex, age (in five-year groups) and calendar year of observation (in 5-year intervals). The stratum-specific numbers of accumulated person-years were multiplied by the cancer incidence rates in the corresponding strata, observed in the entire Swedish population. The number of mid-year population without a previously reported cancer was used as the denominator to compute the incidence rates. The 95 % confidence intervals (CIs) for the SIRs were calculated assuming that the observed events followed a Poisson distribution.[26] Stratified analyses were performed by follow-up duration, sex, presence of complications (bleeding or perforation) at index hospitalization, calendar period of index hospitalization (before vs. after 1980), age at entry (<50, 50-69, 70-) and the calendar period of follow-up (before vs. after 1995). We also estimated relative effects on the SIRs using a multivariate Poisson regression method to compare relative risks among strata, assuming multiplicative effects between outcome and explanatory variables.

All statistical analyses were performed with SAS, release 8.2 (SAS Institute, Cary, NC). Proc GENMOD was used for Poisson regression and the logarithm of the expected number of cases was used as offset variable. All statistical tests were two-sided.

4.4. Study III

The methodology used in this register-based retrospective cohort study was almost the same as the methodology of study II with a few modifications, as described below. Since 1970 the Swedish Cancer Register has used a special code to indicate tumors located in the stomach cardia, therefore, we used the data from 1970 and later to be able to calculate the relative risks separately for two different sub-sites of stomach cancer. Records with NRNs that could not be located in any of these registers (n=4,536) were regarded invalid and excluded. We further excluded 22,851 patients with diagnoses of any cancer before or at the time of the index episode, 12,232 individuals who died during the index hospitalization and 1,912 records due to inconsistencies revealed during data editing and record linkages. Finally our study included 176,017 individuals for further analysis.

Besides unoperated patients, individuals who underwent gastric resection or vagotomy for gastroduodenal ulcer were also followed from the time of surgery until the date of emigration, death, a diagnosis of any cancer, any subsequent gastric surgery or until December 31, 2003, whichever occurred first.

Person-time accrued and cancer events observed during the first year of follow-up were not counted in the analyses, since prodromal cancer symptoms are likely to increase the probability of hospitalization for any known prevalent disease, including peptic ulcer, leading to selection bias in the first year. Further, cancers that are mistaken for benign ulcers will artificially influence the cancer rates in the first year.

To explore the effects of gastric resection and vagotomy on the risk of stomach cancer among duodenal ulcer or gastric ulcer patients we made internal comparisons between the various subcohorts. We first split the data by type of surgical treatment, if any, and follow-up time after surgery (≤10 years vs. >10 years), then calculated relative risks using multivariate Cox proportional hazards regression model assuming multiplicative effects between explanatory variables and outcome (stomach cancer). Attained age (underlying time scale), and sex were included in the regression models.

All statistical analyses were performed with SAS, release 8.2 (SAS Institute, Cary, NC); PROC PHREG was used for the regression model. All statistical tests were two-sided.

4.5. Study IV

This study was based on the data from the Swedish Multi-Generation Register.

The Swedish Multi-Generation Register

The Swedish Multi-Generation Register includes index persons who have been registered in Sweden at some time since 1961 and those who were born in 1932 or later, with links to their biological parents.[215] The Multi-Generation Register is part of the register system for Total Population Register, where information comes from parish civil registration offices before 1991, and the Swedish Tax Agency thereafter. In year 2000 a special supplementary data retrieval was done to make up for the shortfalls in the data on family relations, as parish civil registration offices deleted the deceased individuals together with their linkages to their parents. A new version of the register is created annually, including new index persons who immigrated or were born during the year. For 97% of index persons who were born in

Sweden the information on their mothers has been registered and the corresponding figure is 99% if they were born after 1950. [215]

4.5.1. Subjects

Women born in 1925 or later and who were alive and registered in the population register in 1947, when the National Registration Numbers (NRNs) were introduced, constituted our cohort. The NRN was used for unambiguous linkages with several nationwide registers. The Total Population, Migration, and Causes of Death registers were used to obtain information about marital status, as well as dates of emigration and death. In the Swedish Cancer Register the ICD7 code 151 (stomach cancer) was further broken down into cardia and non-cardia cancer using a supplementary code that was introduced in 1970. Therefore – and since stomach cancer rarely occurs at young ages – the follow-up that formed the study base for the present nested case-control study started on January 1, 1970 or thereafter at age 30 years. After exclusion of subjects with any cancer diagnosed before the start of follow-up, 2,406,439 women were enrolled. Follow-up continued until the date of diagnosis of any cancer, emigration, death, or until December 31, 2004, whichever occurred first. For every observed incident case of stomach cancer we randomly selected five controls, individually matched by year of birth, alive at the time of diagnosis of their matched cases, and without any cancer history before the selection.

4.5.2. Exposure information

The Swedish Multi-Generation Register provided information on number of births and age at first birth. We further linked all cases and controls to the Swedish National Censuses and Education Register in order to obtain information about occupational classes and educational level as markers of socioeconomic status. We used the highest occupational class and education level achieved before the time of selection in our analyses.

4.5.3. Statistical analyses

We used conditional logistic regression models to estimate odds ratios (ORs) with their corresponding 95% confidence intervals (CIs) as the measure of association between parity or age at first birth and risk of stomach cancer. We first estimated crude odds ratios (inherently adjusted for year of birth), then multivariably adjusted odds ratios with additional adjustment for education (categorized into 3 groups, i.e. obligatory 9 years education or less, high school education, and college education or more) and occupational class (categorized into 4 groups, i.e. non-manual workers, self employed, manual workers, farmers and others). Moreover, we considered place of residence (in three regions; south, middle, and north of Sweden) as a possible confounder, but because further adjustment for this variable did not materially affect our estimates, it was not included in the final multivariable models.

We further studied the importance of number of children (1, 2, 3, and >3). Age at first birth was categorized based on the quartile values derived from the entire cohort (<21, 21-24, 25-27, and ≥28 years). Dose-response relationships were studied among ever-parous women only, and the multivariable models were mutually adjusted for number of children and age at first birth. We used median values of age at first birth for each stratum and also number of children as a continuous variable for trend analyses. Women were categorized as pre- or post-menopausal by

using age 50 as the cut-point, based on the approximate median value reported from several previous studies.[216-218]

As the Swedish Multi-Generation Register only includes offspring born in 1932 or later and who were alive in 1961, there is a possibility of missing information about deceased children born between around 1940 (when the mothers in the cohort become sexually mature) and 1961. This could lead to some misclassification. Therefore, we further performed an additional analysis restricted to women born in 1946 or later and thus unlikely to have given birth to children before 1961.

It is well known that unmarried status and living as a single is associated with poorer general health among both men and women, including higher risks for lifestyle-related cancers such as stomach cancer. Therefore, we reanalyzed the data after imposing a restriction to cases and controls who were married at the time of stomach cancer diagnosis (this time was also applied for their corresponding controls) to check if our results had been affected by marital status.

The P value of the interaction term in the conditional logistic regression model was used as a test of homogeneity to compare the odds ratios between pre- and post-menopausal women. All statistical analyses were performed using the SAS software version 9.1 (SAS institute, Cary, NC).

5. Results

5.1. Study I

In this study we found three main dietary patterns among the control group. The first dietary pattern was characterized by high intake of food items which are generally thought to be healthy including vegetables, tomatoes, fruits, fish, and poultry, and was thus labeled as "healthy diet", while the second dietary pattern, labeled as "Western diet", was characterized by high consumption of processed meat, red meat, sweets, high-fat dairy and high-fat gravy. The third pattern was one that loaded heavily on alcoholic beverages including beer and liquor, and French fries and was arbitrarily labeled "alcohol drinker" to be comparable to previous studies. Table 2 shows correlations between a selection of food groups and the three patterns with eigenvalues greater than 1.5.

We did not find any obvious differences of distribution of symptomatic gastroesophageal reflux across any of the three dietary patterns. Subjects who had high factor scores for the "healthy diet" were less likely to be smokers, while those having high "Western diet" scores, on average, had higher body mass index and total energy intake. Subjects having high "alcohol drinker" scores were more likely to be smokers, and have low body mass index or total energy intake.

Table 2. Correlation coefficients between selected food groups and dietary patterns assessed by factor-loading matrix among controls[1]

	Healthy diet	**Western diet**	**Alcohol drinker**
Vegetables	0.76	.	.
Tomatoes	0.61	-0.26	.
Fruits	0.56	.	-0.22
Fish	0.50	0.17	.
Poultry	0.48	.	.
Processed meat	.	0.59	0.24
Red meat	0.23	0.50	0.37
Sweets	0.17	0.49	-0.37
High fat dairy	-0.21	0.47	.
High fat gravy	.	0.41	.
Beer	.	.	0.60
French fries	0.18	0.19	0.54
Liquor	.	.	0.47

[1] Values < 0.15 were not shown in the table for simplicity; those with loadings > 0.40 were underlined.

After controlling for the potential confounding factors – age, sex, symptomatic gastroesophageal reflux, years of education, body mass index, smoking (pack-years), physical activity, and total energy intake – "healthy diet" pattern was, in general, associated with a non-statistically significant moderate reduced risk for the three cancer types under study (Table 3). In contrast, "Western diet" pattern was associated with an obviously increased risk for stomach cardia adenocarcinoma (highest vs. lowest tertiles, OR=1.8, 95%CI 1.1-2.9, p value for trend=0.04), and a modestly increased risk for esophageal adenocarcinoma. Subjects who had highest "alcohol drinker" scores had a more than 3-fold increased risk for esophageal squamous cell carcinoma, compared with those who had the lowest scores.

Table 3. The odds ratios (ORs) and their 95% confidence intervals (CIs) for adenocarcinoma and squamous cell carcinoma of the esophagus, and adenocarcinoma of the stomach cardia by tertiles of dietary patterns scores[1]

	Esophageal adenocarcinoma	Esophageal squamous cell carcinoma	Stomach cardia adenocarcinoma
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Healthy diet			
Low	Reference	Reference	Reference
Medium	0.6 (0.4-0.98)	0.8 (0.5-1.3)	1.0 (0.7-1.4)
High	0.8 (0.5-1.3)	0.7 (0.4-1.2)	0.7 (0.5-1.1)
P value for trend	0.43	0.20	0.13
Western diet			
Low	Reference	Reference	Reference
Medium	1.3 (0.8-2.2)	0.9 (0.6-1.6)	1.7 (1.1-2.6)
High	1.6 (0.9-3.1)	0.7 (0.4-1.4)	1.8 (1.1-2.9)
P value for trend	0.13	0.33	0.04
Alcohol drinker			
Low	Reference	Reference	Reference
Medium	1.0 (0.6-1.6)	2.0 (1.2-3.6)	0.9 (0.6-1.3)
High	0.9 (0.5-1.5)	3.5 (1.9-6.3)	0.8 (0.6-1.2)
P value for trend	0.65	< 0.0001	0.39

[1] Odds ratios were adjusted for age, sex, symptomatic gastroesophageal reflux, years of education, body mass index, smoking, physical activity, and total energy intake.

5.2. Study II

In total there were 61,548 un-operated patients with duodenal ulcer (64.5% male) in the final cohort who contributed 524,960 person-years and 81,379 un-operated patients with gastric

ulcer (52.6% male) who contributed 576,458 person-years. The reason for hospitalization was bleeding for 49% and perforation for 9% of the duodenal ulcer patients, while the corresponding percentages were 47% and 9% for those with gastric ulcer.

5.2.1. Duodenal ulcer

Among un-operated patients with duodenal ulcer followed for an average of 9.1 years, esophageal adenocarcinoma occurred in 27 patients after the first year of follow-up indicating a statistically significant 70% excess risk (Table 4). Upon stratification, the SIRs tended to be slightly higher and statistically significant only during year 2-10 of follow-up, but the point estimate, although based on small numbers, remained above unity also after more than 10 years. We found a borderline significant 30% excess risk of esophageal squamous cell carcinoma in comparison with the matching general Swedish population.

Table 4. Standardized incidence ratios (SIRs) and their 95% confidence intervals (CIs) for esophageal cancer by histology among non-operated patients with duodenal ulcer[1]

	Adenocarcinoma	**Squamous cell carcinoma**
	SIR (95%CI)	SIR (95%CI)
Overall	1.7 (1.1-2.5)	1.3 (1.0-1.8)
Follow-up duration, years		
2-10	1.9 (1.1-3.1)	1.6 (1.1-2.2)
11+	1.5 (0.7-2.8)	0.9 (0.5-1.6)
Calendar year of index hospitalization		
1965-1979	2.1 (1.0-3.8)	1.3 (0.8-2.1)
1980-2003	1.6 (0.9-2.5)	1.3 (0.9-2.0)

[1] First year of follow-up excluded

5.2.2. Gastric ulcer

During follow-up for an average of 7.2 years among 81,379 un-operated patients with gastric ulcer no change in the esophageal adenocarcinoma risk was observed from year two and onwards (Table 5). In contrast, we observed a significant 80% increase in the relative risk of esophageal squamous cell compared to the age, sex and calendar-period matched general population. The excess was slightly more marked among men compared to women, and among younger patients compared to older, with a significant age-wise trend ($p<0.01$).

Table 5. Standardized incidence ratios (SIRs) and their 95% confidence intervals (CIs) for esophageal cancer by histology among non-operated patients with gastric ulcer[1]

	Adenocarcinoma	**Squamous cell carcinoma**
	SIR (95%CI)	SIR (95%CI)
Overall	1.1 (0.6-1.7)	1.8 (1.4-2.3)
Follow-up duration, years		
2-10	1.1 (0.6-2.0)	1.8 (1.3-2.4)
11+	1.0 (0.4-2.2)	1.9 (1.2-2.9)
Calendar year of index hospitalization		
1965-1979	1.0 (0.3-2.4)	1.9 (1.2-2.8)
1980-2003	1.1 (0.6-1.9)	1.8 (1.3-2.4)

[1] First year of follow-up excluded

5.3. Study III

In this retrospective cohort study we had four sub-cohorts including 59,550 unoperated duodenal ulcer patients (64.2% male), 79,412 unoperated gastric ulcer patients (52.3% male), 12,840 patients with partial gastric resection (59.0% male) and 8,105 patients with vagotomy (69.8% male). Overall, patients who underwent surgical treatment were younger than unoperated patients and followed for a longer time. About half of the ulcer patients were hospitalized due to bleeding and about 10 percent due to perforation.

5.3.1. Duodenal ulcers

Among the unoperated patients with duodenal ulcer followed for an average of 8.8 years no significant change in the relative risk of stomach cardia cancer was observed (Table 6). Non-cardia stomach cancer was diagnosed less often than expected with a relative risk of 0.5 compared to the age, sex and calendar-period matched general population.

Table 6. Standardized incidence ratios (SIRs) and their 95% confidence intervals (CIs) for stomach cancer by sub-site among non-operated patients with duodenal ulcer[1]

	Cardia Cancer	**Non-Cardia Cancer**
	SIR (95%CI)	SIR (95%CI)
Overall	1.2 (0.8-1.7)	0.5 (0.4-0.7)
Follow-up years		
2-10	1.4 (1.0-2.1)	0.6 (0.5-0.7)
11+	0.8 (0.4-1.5)	0.5 (0.3-0.7)
Calendar year of index hospitalization		
1970-1979	0.6 (0.2-1.3)	0.6 (0.5-0.8)
1980-2003	1.5 (1.0-2.1)	0.5 (0.4-0.7)

[1] First year of follow-up excluded

5.3.2. Gastric ulcers

An average of 7.0 years of follow-up of unoperated patients with gastric ulcer revealed a significant 90% excess risk of stomach cardia cancer (Table 7). During the same follow-up period, 462 non-cardia stomach cancers were registered which was more than twice the expected number. The relative excess tended to be higher among patients entering the cohort early in the study period, and among those who belonged to the younger age strata at entry.

Table 7. Standardized incidence ratios (SIRs) and their 95% confidence intervals (CIs) for stomach cancer by sub-site among non-operated patients with gastric ulcer[1]

	Cardia cancer	**Non-cardia cancer**
	SIR(95%CI)	SIR(95%CI)
Overall	1.9 (1.5-2.5)	2.1 (2.0-2.4)
Follow-up years		
2-10	2.1 (1.6-2.8)	2.2 (1.9-2.4)
11+	1.6 (0.9-2.5)	2.1 (1.7-2.5)
Calendar year of index hospitalization		
1970-1979	2.2 (1.4-3.4)	2.4 (2.1-2.8)
1980-2003	1.8 (1.3-2.5)	2.0 (1.8-2.2)

[1] First year of follow-up excluded

5.3.3. Surgical treatment

In Table 8 relative risks, estimated with Cox proportional hazards regression modeling, and SIR values, i.e. the relative risks in each sub-category relative to the age, sex, and calendar period-matched general population, are shown for comparison.

Overall, duodenal ulcer patients who had undergone gastric resection had a statistically significant 60% risk elevation compared with unoperated ones, and there was a tendency towards increasing risk with longer follow-up. A statistically non-significant 30% increase in risk of non-cardia cancers was noted also among those who had been subjected to vagotomy, but it appeared as if the excess was confined to the first 10 years after the operation.

In a direct comparison between operated and unoperated gastric ulcer patients, the former had a statistically significant 40% risk reduction relative to the latter. This risk reduction was slightly smaller when more than 10 years had elapsed after the operation.

Table 8. The relative risks (RRs) of non-cardia stomach cancer among operated ulcer patients, relative to unoperated ones with the same ulcer type and relative to general population (SIR). The first year of follow-up was excluded in all analyses.

	Non-cardia cancer	
	RR(95%CI)[1]	SIR(95%CI)[2]
Duodenal ulcer		
Partial resection		
Not operated	Reference	0.5 (0.4-0.7)
Operated overall	1.6 (1.0-2.5)	0.8 (0.5-1.2)
year 2-10 of follow-up	1.3 (0.6-2.7)	0.6 (0.3-1.2)
year 11+ of follow-up	1.7 (1.0-3.0)	1.0 (0.6-1.6)
Vagotomy		
Not operated	Reference	0.5 (0.4-0.7)
Operated overall	1.3 (0.8-2.1)	0.8 (0.5-1.3)
year 2-10 of follow-up	2.0 (1.1-3.7)	1.2 (0.7-2.1)
year 11+ of follow-up	0.8 (0.4-1.7)	0.5 (0.2-1.1)
Gastric ulcer		
Partial resection		
Not operated	Reference	2.1 (2.0-2.4)
Operated overall	0.6 (0.5-0.8)	1.2 (0.9-1.6)
year 2-10 of follow-up	0.6 (0.4-0.9)	1.0 (0.7-1.5)
year 11+ of follow-up	0.7 (0.5-1.0)	1.5 (1.0-2.1)

[1]Estimated from Cox proportional hazards regression modeling, adjusted for attained age and sex.
[2]Risks relative to the age, sex, and calendar period-matched general population.

5.4. Study IV

We identified 2,498 women with non-cardia stomach cancer and 286 women with cardia cancer between 1970 and 2004, and we chose 12,490 and 1,430 matched controls, respectively. The mean age of cases with non-cardia stomach cancer was slightly lower (57.0) than that of cases with cardia cancer (59.4).

5.4.1. Non-cardia stomach cancer

Ever-parous women had the same risk for non-cardia stomach cancer as nulliparous women (OR=0.99, 95% CI 0.87-1.13) (Table 9). However, in an analysis with pre-menopausal non-cardia stomach cancer as the outcome, parity was associated with a reduced odds ratio of borderline significance (OR=0.80, 95% CI 0.63-1.01). The p-value of the test of homogeneity of results pertaining to pre- and post-menopausal cancer was 0.02. Analyses by number of children or age at first pregnancy among ever-parous women did not show any significant variation in relative risks. Restriction to married women did not unveil any important departure from overall results, nor did restriction to women born in 1946 or later.

Table 9. Association of parity with risk of non-cardia stomach cancer among Swedish women[1]

Reproductive variables	All non-cardia stomach cancer		Pre-menopausal cancer[2]		Post-menopausal cancer[2]	
	Cases	Odds Ratio (95% CI)	Cases	Odds Ratio (95% CI)	Cases	Odds Ratio (95% CI)
All women						
Nulliparous	335	Reference	117	Reference	218	Reference
Ever-parous	2163	0.99 (0.87-1.13)	611	0.80 (0.63-1.01)	1552	1.08 (0.92-1.26)
Married women						
All married women						
Nulliparous	53	Reference	19	Reference	34	Reference
Ever-parous	772	1.12 (0.78-1.60)	198	0.75 (0.38-1.47)	574	1.28 (0.84-1.96)
Ever-parous married women						
1 child	148	Reference	26	Reference	122	Reference
>1 child	624	0.94 (0.73-1.19)	172	1.05 (0.58-1.91)	452	0.90 (0.68-1.17)

[1] Adjusted for occupational class and education level.
[2] Attained age ≥50 years was used to define postmenopausal women.

5.4.2. Cardia cancer

We found a 29% decreased risk of cardia cancer among ever-parous women compared to those who never gave birth to a child (OR=0.7, 95% CI 0.5-1.0) (Table 10). This inverse association was statistically significant only for post-menopausal cardia cancer (OR=0.7, 95% CI 0.4-0.99), but the trend with number of children was significant (p=0.04) only for pre-menopausal cardia cancer (although based on small numbers). No conspicuous variation was observed in relation to age at first pregnancy. Restriction to cases and controls who were married at the time of stomach cancer diagnosis revealed an even stronger association (OR for cardia cancer overall =0.4, 95% CI 0.2-0.97 and for post-menopausal cardia cancer =0.4, 95% CI 0.1-0.9), while restriction to women born in 1946 or later disclosed no noteworthy change in the results, albeit based on very small numbers (data not shown).

Table 10. Association of parity with risk of cardia cancer among Swedish women [1]

Reproductive variables	All cardia stomach cancer		Pre-menopausal cancer[2]		Postmenopausal cancer[2]	
	Cases	Odds Ratio (95% CI)	Cases	Odds Ratio (95% CI)	Cases	Odds Ratio (95% CI)
All women						
Nulliparous	46	Reference	7	Reference	39	Reference
Ever-parous	240	0.7 (0.5-1.0)	53	0.9 (0.4-2.2)	187	0.7 (0.4-0.99)
Ever-parous women						
Number of children [3]						
1 child	53	Reference	15	Reference	38	Reference
>1 child	187	0.7 (0.5-0.99)	38	0.6 (0.3-1.2)	149	0.7 (0.5-1.1)
2 children	87	0.6 (0.4-0.9)	25	0.6 (0.3-1.4)	62	0.6 (0.4-0.9)
3 children	62	0.8 (0.5-1.2)	9	0.3 (0.1-0.97)	53	0.9 (0.5-1.5)
≥4 children	38	0.9 (0.5-1.5)	4	0.4 (0.1-1.5)	34	1.1 (0.6-2.0)
p for trend		0.96		0.04		0.31
Married women						
All married women						
Nulliparous	12	Reference	0	Reference	12	Reference
Ever-parous	89	0.4 (0.2-0.97)	18	Not applicable	71	0.4 (0.1-0.9)
Ever-parous married women						
1 child	14	Reference	2	Reference	12	Reference
>1 child	75	0.8 (0.3-1.8)	16	0.3 (0.02-3.4)	59	0.8 (0.3-1.9)

[1] Adjusted for occupational class and education level.
[2] Attained age ≥50 years was used to define postmenopausal women.
[3] Adjusted for occupational class, education level and age at first birth.

6. Discussion

6.1. Methodological considerations

There are many definitions for "epidemiology" but maybe the most popular and accepted one describes epidemiology as the study of the distribution and determinants of disease frequency in human beings.[219, 220] In epidemiological studies the main focus is on the occurrence of disease and other health outcomes and the ultimate goal is to elaborate the causes which explain patterns of these outcomes.[220] Scientific hypothesis testing, posed as qualitative proposition, is the common approach in epidemiological research.

As experimental studies in humans are principally unethical and/or impractical due to known or unknown toxic effects of exposures, scarcity of diseases and long latency period, epidemiological studies can be helpful to investigate the etiology of diseases. Randomized clinical trials are known as the gold standard of scientific studies on human diseases, however, the majority of hypotheses are not testable with this design. For instance, it is not possible to allocate the study population to two different groups and expose one of them to N-nitroso compounds to test if it increases stomach cancer risk as this substance might be carcinogenic. Furthermore, even if there is no harmful effect, a long latency period between exposure and occurrence of disease makes it impossible to find the accurate effect of exposures. Due to the limitations of randomized clinical trials, other epidemiological designs such as case-control and cohort studies have been widely used. These observational studies try to reveal causal relations on the basis of associations between particular exposures and outcomes. However, causal inference in epidemiologic investigations should be done with caution as the observed association might be the result of confounding, different sources of bias, or simply be a chance finding.

6.2. Study design

Non-experimental epidemiological studies can be assigned to three different groups based on their main focus, namely descriptive, analytic and ecological studies. Epidemiological studies in which the frequency of disease, death due to a particular disorder in a population or characteristics of the population and the risk factors are estimated are known as descriptive studies. While these types of studies help to generate hypothesis, the focus of analytic studies – case-control and cohort studies – is the causal association between exposure and outcome. In the latter study design investigators get information on exposure and outcome on an individual level. In ecological studies the association between exposure and outcome are investigated on the population level instead of individual level.

Case-control study

In this study design individuals in the population are classified based on the outcome. In practice after enrolling the patients with the disease of interest, sufficient number of controls will be sampled from the study base which give rise to the cases. Then the information regarding exposure and other important factors is collected from all subjects. If the cases are ascertained from a precisely defined population and the controls are sampled randomly among this population then the study is a population-based case-control study. When the outcome of interest is rare, case-control studies can be helpful to investigate etiologic factors. However,

case-control studies are prone to biases and need to be well-planed from the designing phase to analysis of data.

In matched case-control study design the selection of controls means that they are almost identical to the cases with respect to the distribution of one or more potential confounding factors. The main purpose of matching is to increase efficiency of the study. However, if matching factors are not considered in the analysis it can bias the results. Matching can be individual – i.e. one or more controls with matching factor(s) the same as those in the case – or frequency matching – i.e. an entire stratum of controls with matching factor the same as those in the corresponding stratum of cases.[220] The control subjects, in study I, were frequency matched to the cases for age and sex, and we controlled for these factors in the analyses.

A case-control study can be referred to as a nested case-control when the population which gives rise to the cases is a well-defined cohort and a control series can be selected randomly among the cohort.[220] The nested case-control design preserves the validity of a true prospective cohort study. The reason for this approach is that sometimes more information is needed and it would be too expensive or impossible to get this information for all cohort members. In study IV we used the nested case-control design because it was computationally more convenient in this large data set.

Cohort study

In cohort studies subjects are classified based on the exposure and followed to find the frequency of outcome in different groups. This study design is less suitable for investigating rare diseases. The general population cohort is suitable when the exposure of interest is common,[221] whereas for rare exposures a special exposure cohort is needed such as occupational settings. Cohort studies are principally less susceptible to recall bias and selection bias, but are expensive and time consuming. However, the Swedish health care system and its comprehensive registers – Inpatient Register, Cancer Register, Causes of Death Register, and Migration Register – in which the national registration number is used as a unique identifier, give exceptional opportunities to conduct efficient and relatively cheap register-based retrospective cohort studies.

In studies II and III we linked the mentioned registries to perform retrospective population-based cohort studies. The large sample size with almost complete follow-up is the distinctive strength of these studies. In validation studies with stringent criteria conducted in the Swedish Inpatient Register in 1986 and 1990, errors in the diagnostic data were suspected in 17.3 and 14.2% of the records, while erroneous or missing procedure codes were noted in 9.6%, almost half of which were for minor semi-invasive or auxiliary procedures combined with correctly recorded main procedures.[222] The completeness of the Swedish Cancer Register with reference to stomach cancer is 98% and the false positive rate is 4%. [5] However, the coding of site within the stomach is less trustworthy; the completeness of cardia cancer registration was only 69% and the positive predictive value for cardia cancer was 82% in a relatively recent validation study.[5] However, as expected, most of the time data collected in registers could not cover all the necessary information on potential confounding factors.

6.3. Bias

Bias is any systematic error in epidemiological studies which results in over- or under-estimation of the true association. A bias may happen in selecting the study subjects – selection bias – or the way by which exposure or outcome information is measured/defined – information bias – or when other important related factor(s) influence the results – confounding (see section 6.4).

As information on the exposure is collected after the occurrence of disease in case-control studies a main concern is "recall bias" in which cases recall and report the exposure and/or other important factors differently from controls. This type of information bias is differential misclassification and can bias the relative risk estimates towards unknown direction. In study I, we asked subjects to recall their dietary habits 20 years prior to their interview and it is possible that there were some errors due to failures in memory, but it assured that the symptoms of esophageal and cardia cancer would not influence dietary habits. Moreover, computer aided face-to-face interviews by specially trained professional interviewers from Statistics Sweden held shortly after diagnosis helped to reduce the possibility of recall bias. Presence of different associations between three dietary patterns and three cancer types are reasonable evidence against importance influence from this bias on our results.

As the Swedish Multi-Generation Register includes index persons who have been registered in Sweden since 1961, in study IV there was a possibility of misclassification of exposure due to missed offspring who died before 1961, but additional analyses restricted to women born in 1946 or later suggested that such misclassification is unlikely to have importantly affected our results. However, abortions, miscarriages and stillbirths were not recorded. This misclassification is more likely non-differentia and may have slightly shifted the odds ratios towards the null value.

In "selection bias" the main problem is that for those subjects who are in the study, the association between exposure and outcome is not the same as the association in non-participants. In study I, a well organized case ascertainment system helped to find and register all the incident upper gastrointestinal cancer cases in Sweden between 1994 and 1997. In study IV, we selected our cases using the nationwide Swedish Cancer Register in which case ascertainment was almost complete. Choosing the controls is a critical part of case-control studies. Controls are supposed to be representative of the study base and sampled independently of exposure status. Inappropriate design in this part leads to selection bias by which the true association might be influenced in any direction. Taking advantage of national registration number, we chose the controls for study I and IV randomly among the entire Swedish population. Participation rate for both cases and controls were relatively high in study I. However, in case-control studies there is always a concern about non-participants because their characteristics might differ from those who participated which could bias the results toward an unknown direction.

In studies II and III prodromal symptoms from yet undetected preclinical malignancy may increase the probability of being hospitalized for any known prevalent disease, including peptic ulcer. Therefore, we excluded the first-year follow-up from our analysis to minimize the influence of such selection bias. One limitation in studies II and III is that peptic ulcer has been fairly common in the general population, thus relative risks may have been generally somewhat biased towards the null. Moreover, some of our unoperated patients who entered the cohort in the early part of the study period could well have been operated before they

came into view in the register. Such misclassification will tend to attenuate differences of relative risks between operated and unoperated patients in study III.

Another concern is that it is, practically, difficult to discriminate between cardia stomach cancer and adenocarcinoma of the esophagus. As explained before, documented routines with stringent criteria for the records of the tumors were introduced at all participating sites to reduce misclassification of the tumor site or histologic type in study I. For other studies there is also concern about classification of outcomes as the accuracy in registering cardia cancer and esophageal adenocarcinoma has been reported to be very high in the Swedish Cancer Register.[5, 15] However, this misclassification is non-differential and tends to bias the association toward the null.

6.4. Confounding

A variable must meet three criteria to be counted as a confounding factor.[220] First, a confounding factor must be associated with the exposure of interest, essentially, in the source population. Secondly, a confounding factor must be a risk factor for the disease under study. The association does not need to be causal and the variable can be a marker of a causal factor. Finally, a variable must not be an intermediate factor in the pathway from exposure to outcome to be considered as a confounding factor.

It is necessary to keep in mind that the size of confounding, as a systematic error, should be considered rather than its actual presence.[220] The magnitude of a confounding depends on different factors, i.e. the strength of the association between confounder and outcome and exposure, direction of association, true relative risk and prevalence of exposure and confounder in the source population. The degree of confounding decreases as prevalence of a confounder shifts towards zero or towards hundred percent. This feature is used in restricted studies to deal with some potential confounders. Another factor is the strength of association between confounder and outcome of interest. Confounding increases with increasing strength of the association between the confounder and outcome. This scenario is almost the same for the relation between confounder and exposure of interest.

The direction of confounding depends on the relative risk of exposure-outcome association (above or under the null) and direction of association of confounder with exposure and outcome. If the exposure is protective – relative risk is less than one – and the associations between confounder and both exposure and outcome are in the same direction, positive or negative, then unadjusted estimate will be underestimated. But when the exposure is protective and the direction of associations of confounder with exposure and outcome are not in the same side, one is positive and another is negative, unadjusted estimate will be overestimated. This phenomenon is exactly opposite when the exposure is not protective and relative risk is more than one.

In study I, we adjusted the relative risks for age, sex, years of education, symptomatic gastroesophageal reflux, body mass index, smoking, physical activity, and total energy intake as they are considered as potential confounders for the association of dietary habits and upper gastroesophageal malignancy. However, residual confounding is a main concern in epidemiological studies. Although we cannot rule out this possibility, it is not conceivable that such confounding could completely explain our results.

In study II, tobacco smoking is a confounding factor but as the associations of smoking with both duodenal ulcer and esophageal adenocarcinoma are not strong, it is unlikely to inverse a protective effect, reported in studies on association of *H. pylori* infection and esophageal adenocarcinoma.[42-44, 223] Furthermore, we used the data to estimate, indirectly, the prevalence of smoking in the cohort members by investigating the lung cancer risk and found a moderate association suggesting comparably weak links between smoking and un-operated duodenal ulcer in our cohort. Additionally, NSAIDs such as aspirin are associated with both peptic ulcer and esophageal adenocarcinoma and could therefore be seen as a confounder. However, since these drugs seem to be protective for the outcome and positively associated with the exposure they could not inverse a suggestive negative association between duodenal ulcer and esophageal adenocarcinoma.

In study III, we did not have information about a number of possible confounding factors such as smoking, diet, and drug use. In this study NSAID use is also a potential confounding factor, but because it is protective,[124] it could not explain the results of unoperated cohorts. In the operated gastric ulcer cohort we observed a 40% protective effect which might be partly due to confounding by NSAID use because this factor is positively associated with the exposure and negatively with the outcome. In contrast, confounding by smoking could cause an underestimation of true association as it is positively associated with both risk of operation and stomach cancer.[224] However, the strength of association of the mentioned confounding factors with exposure and outcome is moderate and even if the only explanation for the difference in risk between operated and unoperated patients was confounding, one should explain the reason for the differential effects in duodenal ulcer and gastric ulcer.

In study IV, an important limitation is the lack of information on some important confounding factors, namely smoking, body mass index and gastroesophageal reflux. Smoking is a risk factor for stomach cancer, and it is conceivable that women change their smoking habits when they become mothers. Therefore, confounding by tobacco smoking is a viable possibility. However, available data from other large cohorts of Swedish women revealed no difference in the prevalence of smoking in parous and nulliparous women.[225] To corroborate this, we compared the incidence of lung cancer among our ever-parous and nulliparous cohort members and found an age-adjusted relative risk close to unity (RR=1.04, 95% CI 0.97-1.11). Therefore, confounding by smoking cannot explain the lower risk of cardia cancer among ever-parous women. High body mass index and gastroesophageal reflux disease are other risk factors for cardia cancer, and pregnancy is linked to overweight, obesity,[226] and gastroesophageal reflux disease.[133] However, confounding by high BMI and reflux disease, if any, should have increased the risk of cardia cancer among parous women and does not explain the inverse association. Since obesity and gastroesophageal reflux are essentially unrelated to the risk of non-cardia stomach cancer, it is unlikely that confounding from these factors have materially affected the association between parity and this malignancy.

6.5. Chance

Another type of error in epidemiological studies is random error or chance. The problem comes from the fact that extremely rare events may possibly happen by chance and since effect estimates in epidemiological studies are derived from samples, this error is a main concern. Statistical methods have been used to speculate whether or not the findings can be due to chance. P-value is the value which shows the probability of having the test statistics (association observed in the data) as extreme as, or more extreme than the observed value if

there is no association between the exposure and outcome, assuming no bias in the study.[220] More valuable statistical measure is the confidence interval in which a range of possible values with a particular certainty is calculated and includes the true measure of an association.

Chance finding can be primarily reduced – and thus precision increased – by increasing the sample size. Another important factor that affects study efficiency is the study design with the intention that the proportion of the exposed group, proportion of individuals who develop the outcome of interest, and distribution of subjects based on the important variables is considered.

Although our study is among the largest case-control studies of upper gastrointestinal cancers, in study I we did not have enough cases. Moreover, we did not have enough number of females in this study. This power limitation could result in unstable estimates. Studies II and III are the largest studies to date investigating the association of peptic ulcer diseases and upper gastrointestinal cancers. However, we had limited statistical powers, particularly in the study of the risk of stomach cardia cancer as well as esophageal adenocarcinoma due to low incidence of these malignancies. More problems arose with the stratified analyses and prohibited us from drawing firm conclusions. In study IV we also had limited statistical power particularly in the study of the risk of stomach cardia cancer especially in our stratified analyses.

6.6. General discussion

6.6.1. Role of overall diet in upper gastrointestinal malignancies

We identified major dietary patterns in the Swedish population using factor analysis, and studied their associations with the risk of the three cancer types to enhance understanding of the role of overall diet in the etiology of adenocarcinoma and squamous cell carcinoma of the esophagus, and adenocarcinoma of the stomach cardia. This approach may provide a dietary guideline which could have important public health implications. Of course, due to several possible differences in nutrients between dietary patterns this approach can not be informative about the particular nutrients responsible for the observed differences in cancer risk. Therefore biological relationships between dietary components and disease risk can not be pointed out.

Three patterns were characterized by “high vegetables, tomatoes, fruits, fish, and poultry intake”, “high processed meat, red meat, sweets, high-fat dairy and high-fat gravy intake”, and “high beer, liquor and French fries intake”, respectively. The first pattern was associated with a moderately lower risk of esophageal squamous cell carcinoma, esophageal adenocarcinoma and stomach cardia adenocarcinoma, although statistically not significant. Subjects who scored high for the second pattern tended to have elevated risks for stomach cardia adenocarcinoma and esophageal adenocarcinoma. The third pattern showed a positive and statistically significant association with esophageal squamous cell carcinoma risk.

The results of this population-based case-control study were in the same line as previous findings. It is well established that red meat or fat intake increases the risk of adenocarcinoma of the esophagus or gastroesophageal junction.[31, 33, 35, 227, 228] Moreover, most studies in Western populations also found an inverse association between intake of fresh vegetables and fruits, or nutrient intake derived from these sources, and the risk of adenocarcinoma of the

esophagus, or the gastroesophageal junction,[31, 33, 35, 227-230] as well as the risk of esophageal squamous cell carcinoma.[31, 35, 228] Alcohol intake has been consistently demonstrated as an important and independent risk factor for esophageal squamous cell carcinoma in Western populations,[2] which is also supported by our finding that the "Alcohol drinker" pattern is positively and dose-dependently associated with risk of esophageal squamous cell carcinoma.

6.6.2. Peptic ulcer diseases and esophageal cancer

There is enough epidemiological evidence that *H. pylori* seropositivity has a strong inverse association with the risk of esophageal adenocarcinoma.[42-44, 223] The underlying mechanism of this enigmatic protection is not clear. A hypothesized pathway, in which *H. pylori* may induce atrophic gastritis, hypochlorhydria, and reduction of acid reflux into the esophagus, was not confirmed in two recent studies.[43, 45]

Duodenal ulcer could be seen as a marker of antrum-predominant *H. pylori* infection with hyperchlorhydria, and gastric ulcer could likewise be a marker of *H. pylori* infection, but with a more proximal distribution and a tendency rather towards atrophy and hypochlorhydria. Assuming that atrophic gastritis and hypochlorhydria are not in the pathway of this association, we hypothesized that duodenal ulcer patients and gastric ulcer patients, who are almost invariably infected with *H. pylori*, would have a lower risk of esophageal adenocarcinoma. However, we found, contrary to our expectations, a 70% excess risk for esophageal adenocarcinoma among duodenal ulcer patients, while the relative risk among gastric ulcer patients was close to unity.

The lack of information about factual *H. pylori* status is an important limitation of the present study. Although duodenal ulcer patients are almost invariably infected, one should consider that a non-negligible proportion of our unexposed comparison group, the age, sex, and calendar period-matched general Swedish population, carried antibodies to *H. pylori*. Therefore, whilst studies with individual data on *H. pylori* status compare exposed groups, in which almost 100% are truly infected, with unexposed groups containing close to 0% infected, the corresponding percentages in our study are likely to be 90% versus 50-70%. This will attenuate any measure of association, but it will not reverse them.

In the gastric ulcer analysis the absence of association should not be over-interpreted. The combination of confounding by smoking and attenuation due to "misclassification" of the *H. pylori* status among the supposedly exposed ulcer patients (but only approximately 80% are infected) and the purportedly unexposed comparison population (but with a mean age of 66.7 years at entry probably close to 70% were infected) could conceivably have wiped out a substantial underlying inverse association between *H. pylori* and esophageal adenocarcinoma.

While recent research [43, 45] has challenged the old hypothesis that *H. pylori* protects against esophageal adenocarcinoma via atrophic gastritis and hypoacidity, it appears that our present findings among duodenal and gastric ulcer patients are, again, more in line with the original explanation. The esophageal mucosa in individuals with duodenal ulcer is, on average, more exposed to gastric acid than that in healthy individuals,[231] whereas it is likely to be less exposed in patients with gastric ulcer, linked to corpus gastritis and hypoacidity. According to the old hypoacidity hypothesis, gastric ulcer patients, and those with manifest atrophic gastritis, should be the ones most protected against esophageal adenocarcinoma. As discussed above, the *H. pylori*-associated protection may not be faithfully reflected in the comparison with the general population, and what remains of the effect might have been cancelled by

confounding from smoking. An alternative but admittedly speculative explanation, is that the non-surgical treatment offered to these patients in some way or another modifies the inverse *H. pylori*–esophageal adenocarcinoma relationship.

Previous studies suggested that isolated CagA seropositivity, a possible marker of a previous burned-out infection,[232] as well as clinical or serological indicators of atrophic gastritis may be risk factors for esophageal squamous cell carcinoma.[43, 45] We therefore hypothesized that patients with gastric ulcer, but not those with duodenal ulcer, might have an increased risk for esophageal squamous cell carcinoma. Our results essentially confirmed this hypothesis. In the atrophic, hypoacidic stomach, microorganisms other than *H. pylori* may thrive and generate intragastric nitrosamines.[49] N-nitrosamines are suspected as a key risk factor for esophageal squamous cell carcinoma.[46] Such tumors can be induced by N-nitroso compounds in animal models [50, 51, 233] and endogenous nitrosamines which can reach the esophageal mucosa through one or more unknown ways, such as reflux or via submucosal veins, seem to play a central role.[47] But it should be highlighted that the moderately strong positive association between gastric ulcer and esophageal squamous cell carcinoma could potentially be explained by confounding by smoking, a strong risk factor for this cancer. However, the differential associations for gastric ulcer and duodenal ulcer somewhat disagree with such confounding as the sole explanation.

6.6.3. Peptic ulcer diseases and stomach cancer

The results of study IV revealed that well established risk reduction for stomach cancer among duodenal ulcer patients [78, 201, 234] pertain only to non-cardia stomach cancer and not to cardia cancer. This result is conceivable as the relationship between *H pylori* infection and cardia cancer seems to be weak or non-existing,[3] although there are conflicting results.[234, 235] However, recently it was suggested that cardia cancers may have two different subtypes with distinct etiologic factors,[58] i.e. *H. pylori*-induced atrophic gastritis and short-segment gastroesophageal reflux disease. Hence, this issue should be addressed in future studies. Moreover, the mechanism behind the enigmatic low risk of non-cardia stomach cancer among duodenal ulcer patients – despite of the strong links between duodenal ulcer and *H. pylori* infection and between *H. pylori* and non-cardia stomach cancer – needs to be clarified.

We further found that the risk elevation among gastric ulcer patients occurs for both cardia and non-cardia stomach cancer. While the reason for differential association of duodenal ulcer with two anatomical subtypes of stomach cancer, specifically a protective effect which does not pertain to cardia cancer, remains obscure, a positive association between gastric ulcer and cardia cancer may be expected given the hypothesized special importance of N-nitroso compounds in the etiology of this cancer [236] and the documented increase in nitrite and N-nitrosamine levels in the stomachs of patients with gastric ulcer and/or hypochlorhydria.[237, 238]

6.6.4. Surgical treatment of peptic ulcer and risk of stomach cancer

Numerous studies in the past have addressed stomach cancer risk among patients who have undergone partial gastric resection for peptic ulcer, but the results have not been all consistent.[119, 120] In fact, the results range from a more than twofold increased risk to an 80% decreased risk.[119] But it should be considered that both underlying disease and time since operation are important, and that the risk among duodenal ulcer patients is below expectation for some 20 years, ostensibly due to the reduction of tissue at risk, until it starts to rise.[119] Despite the removal of a substantial part of the stomach, surprisingly, surgically resected

duodenal ulcer patients had an increased risk for non-cardia cancer. This was contrary to the findings among resected gastric ulcer patients, whose risk was below that among unoperated gastric ulcer patients. The reason why resection in gastric ulcer disease reduces stomach cancer risk, while the same resection rather seems to increase the risk already within the first decade in duodenal ulcer patients is unclear. One could speculate that premalignant foci are already common in gastric ulcer patients so that removal of tissue will have an almost immediate effect. It is even conceivable that a non-negligible number of misdiagnosed malignant gastric ulcers remain silent for several years and thus contribute substantially to the increased stomach cancer incidence among unoperated gastric ulcer patients. As no malignant or premalignant foci are expected to be present among duodenal ulcer patients who undergo resection, removal of tissue may not have any noticeable effect in the first decades. Why the risk among resected duodenal ulcer patients is slightly higher than among unoperated still begs an answer. Clearly, chance could be one explanation for our findings. The possibility of confounding by indication must also be entertained, particularly as the excess risk was noticeable already in the first decade after the operation. Factors contributing to complications that may prompt the decision to operate should also be considered; NSAID use is such a factor, but since it is protective,[124] the effect of this confounding is expected to be an even lower risk among operated patients. Smoking may also be such a factor, and it is clearly a risk factor for stomach cancer.[224]

Furthermore, we found that vagotomized duodenal ulcer patients had an increased risk of non-cardia stomach cancer in the first decade after the operation when compared with unoperated patients with the same disease, but this excess disappeared when 10 years had elapsed. Increased risks have been reported previously.[121-123] One could hypothesize that decline in gastric acidity may contribute to intragastric N-nitrosation and subsequent stomach cancer development. However, it would probably take many years before a clinically evident cancer would be diagnosed, and one would expect that the risk would increase gradually with follow-up time well beyond the first decade. Therefore, confounding by factors related to the indication for surgery, for instance smoking, must be considered to be the most likely explanation for our finding.

6.6.5. Parity and risk of stomach cancer

The presence of functional estrogen receptor alpha [127, 128] and beta [129, 130] in human stomach mucosa, and the results from experiments in rodents,[126] prompted us to hypothesize that the lower incidence of stomach cancer among females might be due to a protective effect of sex hormones, particularly estrogen. However, we observed an inverse association of parity with subsequent risk of cardia but not non-cardia stomach cancer.

With adjustment for indicators of socioeconomic status, it is improbable that parity is associated with *H. pylori* infection status unless the latter is related to fertility. And if a relationship between the infection and fertility would indeed exist, the observed inverse association between parity and cardia cancer would be expected only if *H. pylori* infection would be linked to *increased* fertility – a less likely, albeit not totally inconceivable, scenario. However, if infected women would be more fertile, parity is predicted to be positively associated with risk of non-cardia stomach cancer, contrary to our finding.

Among previous studies on stomach cancer risk in relation to reproductive factors, only one recent Canadian case-control study [137] considered cardia cancer and non-cardia stomach cancer

separately. The authors found a decreased risk for both cardia and non-cardia stomach cancer among women with more than three children compared to nulliparous women. However, the number of cases was small (14 cardia and 57 non-cardia stomach cancers) and only the overall relative risk was statistically significant. Other studies on the association between parity and risk of postmenopausal stomach cancer, not considering the anatomical subtypes, found relative risks close to unity among ever-parous compared with never-parous women.[134, 135] However, one cohort study,[141] which used death registry data to find the stomach cancer cases, reported a non-significant inverse association with postmenopausal stomach cancer.

There are inconsistent results regarding the association between number of children and stomach cancer. While two previous studies [137, 141] found suggestive evidence of an inverse relationship with stomach cancer risk but without any significant dose-risk trend, others found no association.[134, 135, 138] Moreover, one hospital-based case-control study [136] and two other studies without adjustment for socioeconomic status [139, 140] reported a positive association. In the present study comparing women with more than one child to those with one child showed a borderline significant 30% risk deficit for postmenopausal cardia cancer. However, the absence of a significant dose-response trend somewhat contradicts a causal inference. On the other hand, there was a significant dose-risk trend for premenopausal cancer, while only one relative risk estimate among single exposure categories attained statistical significance.

There are inconsistent reports on the association between stomach cancer risk and age at first birth. Previous studies reported both increased [135, 141] and decreased [134, 136] stomach cancer risks among women with higher age at first birth compared to those with lower age. We did not find any significant variation in the risk of cardia or non-cardia stomach cancer linked to age at first birth.

To our knowledge there is no clear biological rationale why the inverse parity-risk relationship should be limited to cardia cancer. Therefore, the hypothesis that sex hormones like estrogen might play a role in the etiology of stomach cancer is given no real support. The diverging result pertaining to cardia cancer might signal that the inverse relationship with parity is mediated by factors other than estrogen and related hormones. On the other hand, parity may be an imperfect marker of the sex hormone exposure that is potentially relevant for gastric carcinogenesis; women are continuously exposed to estrogen during their fertile life, spanning up to 40 years, and the boosts during pregnancies – although impressive in terms of dose – may be too short-lived or inadequately timed for a noticeable biologic effect on gastric precancerous processes.

This study gave no indication of any important inverse association between parity and risk of non-cardia stomach cancer. As it is very unlikely that confounding from known but unmeasured lifestyle-related risk factors has cancelled a true inverse association, our results make a fairly persuasive case against a significant inhibitory role of estrogen during the development of human non-cardia stomach cancer. Previous evidence of an inverse association between markers of female sex hormone levels and stomach cancer risk was, at best, suggestive and the present combined literature (including our study) weighs towards no association. However, our finding of a significantly decreased risk of cardia cancer among parous women, particularly among postmenopausal ones, observed also by other investigators, warrants further studies. Although the smaller observed numbers of cardia cancer increase the scope for chance variations, the discrepancy between cardia and non-cardia cancer might indicate that the risk reduction is mediated by factor(s) that affect cancer development in the cardia and in the rest of

the stomach differently. Gastrooesophageal reflux, obesity, and *H. pylori* infection are unlikely candidates, though.

7. Conclusion

- A diet rich in vegetables, tomatoes, fruits, fish, and poultry seems to decrease the risk of both histologic subtypes of esophageal cancer and stomach cardia adenocarcinoma, while a diet including high consumption of processed meat, red meat, sweets, high-fat dairy and high-fat gravy increases the risk of esophageal adenocarcinoma and stomach cardia adenocarcinoma. The dietary pattern characterized by high alcohol (beer and liquor) intake significantly increases the risk of squamous cell carcinoma of the esophagus.

- The well-established strong inverse association of *H. pylori* seropositivity and risk of esophageal adenocarcinoma does not pertain to all infections. It seems that the pattern of gastric colonization and/or the clinical consequences in the stomach is a key factor in this pathway.

  It seems that a positive association exists between gastric ulcer and risk of esophageal squamous cell carcinoma, suggesting a key role of corpus atrophy on esophageal squamous cell carcinoma etiology.

- Gastric ulcer patients have an increased risk for both anatomical subtypes of stomach cancer, whereas duodenal ulcer patients have a reduced risk only for non-cardia cancer. Although the mechanisms behind the differential relationships between duodenal ulcer disease and stomach cancer of cardia and non-cardia location remain unknown, an analogous differential association between *H. pylori* infection and these two types of cancer suggests that the underlying *H. pylori* infection might play a pivotal role also for the protection.

  Partial gastric resection appears to increase the risk of non-cardia stomach cancer among duodenal ulcer patients, but to reduce risk among those with gastric ulcer.

- Exposure to female sex hormones is not associated with protection against non-cardia stomach cancer and does not seem to explain the male predominance for such cancer. However the observed moderate inverse relationship between parity and cardia cancer might be mediated by other factors than hormonal and warrants further studies.

8. Future studies

Despite of considerable efforts to improve treatment of esophageal and stomach cancers, as well as expansion of knowledge about their etiology, these malignancies remain a challenge to health care system worldwide. The work presented in this thesis answered some questions about the potential risk factors of upper gastrointestinal cancers. Meanwhile, it raised a number of stimulating questions which seek durable answers to shed revealing light on the mechanism behind these public health problems.

More studies with focus on dietary patterns are needed in other regions, especially high risk area, e.g. “esophageal cancer belt”, to enhance understanding of overall role of dietary factors in the etiology of upper gastrointestinal cancers, as well as to provide a dietary guideline for the sake of public health system.

The mechanism behind differential associations for duodenal ulcer and gastric ulcer with risk of esophageal adenocarcinoma should be addressed in future studies. It would also be interesting to find whether the epidemic of esophageal adenocarcinoma exists or has started to emerge in eastern Asian countries, where shift to western lifestyle has happened in last few decades. Additionally, more studies with careful control of potential confounding factors are needed to confirm the link between *H. pylori* infection and esophageal squamous cell carcinoma. It seems that majority of the *H. pylori* strains in Asian countries with high incidence of esophageal cancer are *cag*A positive. Therefore, studies on the additional virulent factors and modifications in *H. pylori* genome during long term infection are needed.

While the mechanism by which *H. pylori* increases risk of stomach cancer is not clear yet, exploring the reason(s) for well-known enigmatic protective effect of duodenal ulcer on non-cardia stomach cancer might be helpful. Furthermore, differential risks of cardia cancer linked to duodenal ulcer and gastric ulcer diseases urge more investigation to reveal the potential etiologic role of *H. pylori* infection and its mechanism. It seems that interplay between host genetic background, *H. pylori* strain and environmental factors should be the focus of future investigations. The results of such studies may help to find the best intervention strategy. It is suggested that overgrowth of some bacteria in atrophic stomach is an essential step from *H. pylori* infection to stomach cancer. Increasing our knowledge about these organisms would shed further light on our understanding of etiology of stomach cancer and may be helpful for primary prevention.

More studies with detailed information on potential confounding factors, particularly smoking, are needed to verify whether there exists a protective effect of parity on cardia cancer. Moreover, it might be helpful also to study whether estrogen receptors exist in the cardia as well as more distal parts of the stomach.

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