Occupational and socio-economic factors in the etiology of cancer of the esophagus and gastric cardia

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ABSTRACT

Adenocarcinoma of the esophagus and gastric cardia and squamous-cell carcinoma of the esophagus have a poor prognosis. The increasing incidence and the strong male predominance of esophageal and cardia adenocarcinoma are striking, and yet unexplained, patterns that should be due to unknown environmental factors. The main aim of this thesis was to study occupational and socio-economic factors in relation to these tumors.

Papers I, III and IV are based on a nationwide Swedish population-based case-control study where 189 esophageal adenocarcinoma cases, 262 cardia adenocarcinoma cases, 167 esophageal squamous-cell carcinoma cases and 820 frequency-matched controls underwent personal interviews. In paper I, we investigated the role of stressful psychosocial working conditions. We found no influence of job strain, except between one job strain measure and a 2.2-fold (95% CI, 1.0-4.8) increased risk of cardia adenocarcinoma. Having a covert coping style, compared to an overt, was associated with moderately increased risks of both esophageal (OR 1.8, 95% CI, 1.2-2.8) and cardia adenocarcinoma (OR 1.5, 95% CI, 1.0-2.2). Low work pace satisfaction was associated with about 3-fold increased risks of both histological types of esophageal cancer. Thus, work-related stress does not seem to be associated with the risk of these tumors, while the interplay between a stressful work environment and the individual’s responses to it may influence the risk.

In paper II, we examined airborne occupational exposures among men and risk of esophageal and cardia cancers. We analyzed 12 agents in a prospective cohort study where 260 052 Swedish construction workers were followed 1971 to 2000. We found positive associations between high exposure to asbestos (IRR 4.5, 95% CI, 1.4-14.3) and cement dust (IRR 3.8, 95% CI 1.5-9.6) and risk of esophageal adenocarcinoma, and between high exposure to asphalt fumes (IRR 2.3, 95% CI, 1.0-5.3) and wood dust (IRR 4.8, 95% CI, 1.2-19.4) and risk of cardia adenocarcinoma. No consistent associations regarding esophageal squamous-cell carcinoma were found.

In paper III, the relation between socio-economic status (SES) and risk of esophageal and cardia cancers was studied. Our classification of SES was derived from each participant’s occupational history. The risk of esophageal adenocarcinoma and squamous-cell carcinoma increased with decreasing SES; unskilled workers had 3.7-fold (95% CI, 1.7-7.7) and 2.1-fold (95% CI, 1.0-4.7) increased risks, respectively, compared to professionals. Adjustment for reflux, body mass and smoking attenuated the risk for esophageal adenocarcinoma, while adjustment for H. pylori infection did not influence the results. Life without a partner was associated with over 2-fold increased risks of esophageal adenocarcinoma and squamous-cell carcinoma, associations remaining after multiple adjustments. Thus, both histological types of esophageal cancer are linked to low SES and single life, associations only partly explained by known risk factors.

Finally, in paper IV, we investigated specific airborne occupational exposures in relation to risk of esophageal and cardia cancers. Based on each participant’s occupational history we assessed cumulative airborne exposure for 10 agents, analyzed individually and combined. Further, occupations and industries were analyzed. Tendencies of positive associations between high exposure to pesticides and risk of esophageal (OR 2.3, 95% CI, 0.9-5.7) and cardia adenocarcinoma (OR 2.1, 95% CI, 1.0-4.6) were found. Workers highly exposed to combined particular agents were at a seemingly increased risk of esophageal squamous-cell carcinoma (OR 1.7, 95% CI, 1.0-2.9). There were no other consistent associations. Thus, airborne occupational exposures do not seem to be of major importance in the etiology of esophageal or cardia adenocarcinoma.
LIST OF PUBLICATIONS

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

   Psychosocial working conditions and the risk of esophageal and gastric cardia cancers.
   *European Journal of Epidemiology.* 2004:19;631-641

II. Jansson C, Johansson AL, Bergdahl IA, Dickman PW, Plato N, Adami J, Boffetta P, Lagergren J.
    Occupational exposures and risk of esophageal and gastric cardia cancers among male Swedish construction workers.
    *Cancer Causes & Control.* 2005:16;755-764

III. Jansson C, Johansson AL, Nyrén O, Lagergren J.
    Socioeconomic factors and risk of esophageal adenocarcinoma: A nationwide Swedish case-control study.
    *Cancer Epidemiology Biomarkers & Prevention.* 2005:14:1754-1761

IV. Jansson C, Plato N, Johansson AL, Nyrén O, Lagergren J.
    Airborne occupational exposures and risk of oesophageal and cardia adenocarcinoma.
    *Occupational and Environmental Medicine,* in press

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<td>Adenocarcinoma of the esophagus</td>
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<tr>
<td>AC</td>
<td>Adenocarcinoma of the gastric cardia</td>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>CagA</td>
<td>Cytotoxin-associated gene A</td>
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<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td><em>H. pylori</em></td>
<td><em>Helicobacter pylori</em></td>
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<td>i.e.</td>
<td>That is (<em>id est</em>)</td>
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<td>ICD-7</td>
<td>7th Revision of the International Classification of Diseases</td>
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<td>IRR</td>
<td>Incidence rate ratio</td>
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<td>NRN</td>
<td>National Registration Number</td>
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<td>NYK</td>
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<td>OR</td>
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<td>SCB</td>
<td>Statistics Sweden</td>
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<td>SCC</td>
<td>Squamous-cell carcinoma of the esophagus</td>
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<td>SECC-study</td>
<td>The Swedish Esophageal and Gastric Cardia Study</td>
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<td>SEI</td>
<td>Swedish socio-economic classification</td>
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<td>Swedish Standard Industrial Classification</td>
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<td>SoS</td>
<td>The Swedish Board of Health and Welfare</td>
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<tr>
<td>TLV</td>
<td>Treshold limit value</td>
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INTRODUCTION

The epidemiologic patterns associated with cancer of the esophagus and gastric cardia has changed importantly during recent decades. For reasons yet unknown, the incidence of esophageal adenocarcinoma is increasing dramatically, and the incidence of gastric cardia adenocarcinoma moderately, in the Western world, particularly in men. The rate of increase of esophageal adenocarcinoma is greater than that of any other major malignancy in the United States. In contrast, the incidence of the dominating histological type of esophageal cancer, i.e. squamous-cell carcinoma, has remained stable or declined in Western populations. Further, there is a yet unexplained strong male predominance among patients with esophageal or gastric cardia adenocarcinoma. The rapidity of the increase suggests important influence of environmental factors as etiological agents. Although the survival of these tumors has improved slightly during recent years, the prognosis is still poor, with a relative 5-year survival rate of about 10%. Prevention, based on etiologic research, might therefore be the best way of reducing the mortality of esophageal and gastric cardia adenocarcinoma.

This thesis, including four original papers, investigates the association between occupational and socio-economic factors and the risk of esophageal and gastric cardia cancers, particularly focusing on the adenocarcinomas. Studies of the significance of occupational and socio-economic factors in the etiology of these tumors are rare.
BACKGROUND

CANCER OF THE ESOPHAGUS AND GASTRIC CARDIA; CLASSIFICATION AND DESCRIPTIVE EPIDEMIOLOGY

Classification
There are two main histological types of cancer of the esophagus, each with different risk factors and epidemiology. The dominating type worldwide is squamous-cell carcinoma (1). The other major type is adenocarcinoma. Cancer of the gastric cardia, of which there are virtually only adenocarcinomas, though classified as a type of gastric cancer, has several epidemiological characteristics in common with esophageal adenocarcinoma not shared by more distal gastric cancer, and is therefore included in this thesis.

Occurrence
Esophageal cancer is the eighth most common cancer worldwide and the sixth most common cause of cancer death (1). In 2002, 462,000 new cases were diagnosed, and 386,000 deaths were reported (1). Geographic variation in incidence of esophageal cancer is striking (1, 2). About 80% occur in developing countries (3), of which the majority is squamous-cell carcinomas (1). High-incidence areas include China, southern and eastern Africa and south central Asia (1). In Sweden, about 400 new cases of both histological types of esophageal cancer, and about 200 cases of gastric cardia cancer, are diagnosed per year (4).

During the past three decades the epidemiologic patterns associated with cancer of the esophagus have changed importantly (5). Thirty years ago, esophageal adenocarcinoma was a rare diagnosis worldwide (6). However, since the mid-1970s the incidence of this tumor has increased dramatically in the Western world (5-9). Rising incidence trends have been reported in the United States (10-16), several European countries (17) including Great Britain (18, 19), France (20, 21), Switzerland (22), the Netherlands (23), Denmark (24), Norway (25) and Sweden (26, 27), Australia (28, 29) and New Zealand (30), and the incidence is still rising (6, 16, 31).

In most countries, including Sweden, the rising incidence is particularly evident in men (6, 14, 23, 26, 29, 30). Among white males in the United States the incidence of adenocarcinoma of the esophagus has risen over 350% since the mid-1970’s, surpassing that of squamous-cell carcinoma around 1990 (14). The rate of increase of this tumor in the last 25 years is greater than that of any other major malignancy in the United States (Figure 1) (16), with the absolute incidence increasing six fold from 1975 to 2001, from 4 to 23 cases per million, a relative increase greater than that for melanoma, prostate or breast cancer (16).
There have also been reports of an increase, but at a slower rate, of *gastric cardia adenocarcinoma* in the United States (11-14), several European countries (17, 18, 23, 24), including Sweden (32), and Australia (28). However, stable (22, 25) or declining (30) incidence trends have been reported from Norway, Switzerland and New Zealand. Furthermore, around 1990 the rising incidence of gastric cardia adenocarcinoma has discontinued in Australia, Sweden, Great Britain and the United States (15, 29, 31, 33), and this might be explained, at least partly, by improvements in site classification in the tumor registers (2, 11, 17, 34). Thus, the pattern regarding the incidence trends of gastric cardia adenocarcinoma is somewhat inconsistent.

The increasing incidence of esophageal adenocarcinoma in Western countries, even though a rare disease, is in contrast to the descriptive epidemiology of the dominating histological type of esophageal cancer, i.e. *esophageal squamous-cell carcinoma*. Worldwide, the incidence of esophageal squamous-cell carcinoma has remained stable (7, 20, 22, 25, 29) or declined (14, 16), although slight increases have been reported in Great Britain, Sweden and the Netherlands (18, 19, 23, 26).

Studies confirm that the increasing incidence of esophageal adenocarcinoma is real (14, 16, 34). The rising incidence is unlikely to be explained by changes in classification, not by anatomic reclassification of gastric cardia adenocarcinoma into esophageal adenocarcinoma, because the incidence of gastric cardia adenocarcinoma did not fall at the same time as the incidence of esophageal adenocarcinoma rose (16, 35), nor by histological reclassification of esophageal squamous-cell carcinoma, because the increase is restricted to
the lower third of the esophagus, the site where most adenocarcinomas arise (16). Further,
improved diagnostic methods, with the general introduction of endoscopy, cannot explain
this pattern, since the trends differ significantly between men and women (36), and since
the incidence is still increasing during a period of no or minimal changes of diagnostic
procedures (16). Changes in diagnostic methods or in pathologic classification leading to
reclassification would be expected to be implemented in a relatively limited period, while
the incidence of esophageal adenocarcinoma has been steadily rising over the past three
decades (16).

Age and sex distribution
The incidence of esophageal (both types) and gastric cardia cancer increases with age, with
most patients diagnosed between the ages 55 and 85 (2). Cases occurring below the age of
40 are very rare (2).

There is a strong male predominance among patients with esophageal or gastric cardia
adenocarcinoma (2, 8, 14, 37). The imbalance between men and women is about 7 to 1
(14, 37). These observations have been similar in all populations studied (2, 6, 14, 18, 32).
There is also a male predominance among patients with esophageal squamous-cell
carcinoma, though less pronounced, with a male/female sex ratio of about 3 to 1 (8).

DIAGNOSIS, TREATMENT AND PROGNOSIS
Common symptoms of esophageal or gastric cardia cancer are dysphagia, weight
reduction, bleeding and pain. Symptoms of esophageal or gastric cardia cancer often have
their onset in an advanced tumor stage. Therefore, at the time of initial diagnosis most
patients have an incurable disease, due to dissemination or local advancement of the
cancer. Surgical resection is currently the only potentially curative treatment of patients
with these cancers. This operation is demanding, as is reflected by the high postoperative
morbidity and mortality. For the majority of patients it is important to select the best form
of palliative treatment (38).

Cancers of the esophagus and cardia are aggressive and belong to the cancer types with the
worst prognosis (3, 39). The survival of esophageal cancer has improved slightly during
recent years, but the relative 5-year survival rate is still only about 10% in most Western
populations (5, 39, 40). The chance of survival is the same for the two histological types.
The relative 5-year survival rate for gastric cardia cancer is 10-15% (38). The prognosis is
poor also for patients treated with the intention to cure, when no dissemination of the
cancer has been discovered. Although it recently has been shown that survival after
esophageal cancer surgery has improved, the 5-year survival is still only about 30% (41).
The poor survival rates indicate that all efforts to improve treatment and diagnostic
procedures have only to a limited degree contributed to an improved long-term survival
(42). Prevention, based on etiologic research, might therefore be an effective instrument in
reducing the mortality of cancer of the esophagus and gastric cardia.
FACTORS INFLUENCING ESOPHAGEAL OR GASTRIC CARDIA CANCER RISK

The etiologies of cancer of the esophagus and gastric cardia are likely to be multifactorial (9). The suddenness and the rapidity of the rising incidence of esophageal adenocarcinoma, and the increase across populations, imply important influence of environmental factors as etiologic agents (2, 6, 9, 26, 43). The reasons for the increasing incidence remain essentially unexplained (2, 5, 6, 11, 36, 37, 43). To explain a rise of this magnitude the prevalence of a strong risk factor must also rise dramatically, and such a risk factor has not yet been identified (16). Moreover, the male predominance among patients with esophageal or gastric cardia adenocarcinoma is largely unexplained (2, 14, 44, 45). No studies document sufficient variability of the distribution of known risk factors between genders to account for the differences in adenocarcinoma incidence (2, 45).

Several factors associated with the risk of esophageal or gastric cardia adenocarcinoma have been identified during recent years. In this section, a brief overview of risk factors for these tumors, except old age and male sex mentioned in the previous section, are presented along with factors influencing the risk of esophageal squamous-cell carcinoma.

Esophageal adenocarcinoma

Barrett’s esophagus, a columnar cell metaplasia replacing the normal squamous-cell epithelium in the distal esophagus, associated with gastroesophageal reflux (46), is the strongest risk factor for adenocarcinoma of the esophagus (47), with a majority of cases of esophageal adenocarcinoma arising from Barrett’s esophagus (43).

Gastroesophageal reflux (or reflux symptoms) per se is a strong, independent risk factor for esophageal adenocarcinoma, according to several epidemiological studies of different designs. Strong, positive associations between reflux and esophageal adenocarcinoma have been found in several population-based case-control studies (48-50) and one cohort study (51), with risk increases varying from 2- to 8-fold, or even 43-fold among persons with long-standing and severe reflux symptoms (49).

Gastroesophageal reflux is extremely common in Western societies (52, 53), and the prevalence is increasing (53), but there is a lack of data regarding the incidence of gastroesophageal reflux (54). It is therefore uncertain if reflux symptoms have increased rapidly during recent decades, i.e. preceding the rising incidence of esophageal adenocarcinoma (54). Furthermore, the prevalence of reflux symptoms seems to be similar for men and women (55), i.e. it does not match the skewed sex distribution of esophageal adenocarcinoma well.

Past use of medications relaxing the lower esophageal sphincter, and thereby facilitating reflux, has been positively associated with esophageal adenocarcinoma (56). This association disappeared after adjustment for reflux, indicating that reflux could be a link between the use of these drugs and esophageal adenocarcinoma (56). In the 1960s and 70s use of these medications increased and may have contributed to the rising incidence (56).

High body mass index (BMI) is a strong, independent risk factor for esophageal adenocarcinoma, with positive associations found in case-control studies of esophageal and cardia adenocarcinoma analyzed combined (57), in case-control studies of esophageal adenocarcinoma analyzed separately (58-61) and in one recent prospective study (62), with
risk increases varying between 2-8-fold among overweight (BMI 25-30) and 3-16-fold among obese (BMI > 30).
The increasing prevalence of overweight and obesity in Western countries (59) could be of importance in understanding the increasing incidence of esophageal adenocarcinoma, but the dramatic increase is not entirely consistent with this interpretation (60). Moreover, the male predominance cannot be explained by sex differences in overweight (62).

Infection with gastric *Helicobacter pylori* (*H. pylori*) seems to reduce the risk of esophageal adenocarcinoma, based on findings in several case-control studies where esophageal and cardia adenocarcinoma were combined (63), and where esophageal adenocarcinoma was analyzed separately (64, 65), as well as in a recent prospective study (66), albeit no association was found in one study (67).
The decreasing prevalence of *H. pylori* infection in developed countries (63) coincides with the rising incidence of esophageal adenocarcinoma (64). If the inverse association is causal then it may at least partly contribute to the increase (66).

**Tobacco smoking** is a moderate risk factor for esophageal adenocarcinoma, indicated by positive associations found in several case-control studies combining esophageal and gastric cardia adenocarcinoma (57, 68-70), in case-control studies of esophageal adenocarcinoma analyzed separately (61, 71, 72) and in one prospective study (62), with risk increases ranging between 1.5-3-fold. However, smoking is an unlikely contributor to the rising incidence of esophageal adenocarcinoma, at a time when the incidence of smoking-related tumors such as lung cancer is declining in men, in the United States and Europe (73-75), and considering recent reductions in the prevalence of smoking, particularly among men (73, 74, 76). Thus, tobacco smoking cannot explain the male dominance among patients with esophageal adenocarcinoma (62).

**High dietary intake of fruit and vegetables and antioxidants** seems to be inversely associated with esophageal adenocarcinoma, according to several epidemiological studies (58, 77-80). However, intake of antioxidants cannot explain the divergent incidence rates of esophageal adenocarcinoma and squamous-cell carcinoma, as it reduces the risk of both tumors (78).

**Non-steroid anti-inflammatory medications** may decrease the risk of esophageal cancer, where pooled results from many studies support a protective association between these medications and both histological types of esophageal cancer (81). However, in a recent nested case-control study it was found that confounding by “contraindication” might explain this association due to lack of adjustment for upper gastrointestinal disorders, such as reflux, in most prior studies (82).

**Alcohol intake** is not associated with risk of esophageal adenocarcinoma according to recent well-designed population-based studies (62, 71, 72). In previous case-control studies combining esophageal and gastric cardia adenocarcinoma positive associations were found (57, 68, 69), but in recent case-control studies (61, 70-72) and one prospective study (62) no association has been found.
**Gastric cardia adenocarcinoma**

*Gastroesophageal reflux* is an independent, moderate risk factor for gastric cardia adenocarcinoma, according to several case-control studies (49, 59) and one prospective study (51), with risk increases of about 2-fold.

**High BMI** is another independent, moderately strong risk factor for gastric cardia adenocarcinoma, based on case-control studies of esophageal and gastric cardia adenocarcinoma combined (57), of gastric cardia adenocarcinoma analyzed separately (59-61), and one prospective study (62), with risk increases varying between 1.5-2-fold.

**Tobacco smoking** is a fairly strong risk factor for gastric cardia adenocarcinoma according to earlier case-control studies where esophageal and gastric cardia adenocarcinoma were combined (57, 68-70), as well as more recent case-control and prospective studies analyzing gastric cardia adenocarcinoma separately (62, 71, 72, 83), with risk increases ranging from 2-4-fold.

**High dietary intake of cereal fiber** seems to be inversely associated with gastric cardia adenocarcinoma (68, 84).

**Alcohol intake** is not associated with gastric cardia adenocarcinoma (61, 62, 70-72, 83).

**Esophageal squamous-cell carcinoma**

*Tobacco smoking* and *alcohol intake* are the dominating risk factors for esophageal squamous-cell carcinoma in the Western world, especially when combined (37). These factors have been estimated to be responsible for 90% of all cases in this part of the world (85). Many studies have found strong positive associations between tobacco smoking (57, 71, 72, 86) and alcohol intake (57, 62, 71, 72) and the risk of esophageal squamous-cell carcinoma. The male predominance among patients with esophageal squamous-cell carcinoma is explained by sex differences in the exposure for tobacco and alcohol (87).

**Low consumption of fruit and vegetables** is another risk factor for esophageal squamous-cell carcinoma (78, 88).

The importance of genetic factors in the etiology of esophageal cancer seems to be uncertain. In two case-control studies of familial occurrence, no evidence of a family history of self-reported digestive cancers among cases of both histological types of esophageal cancer or gastric cardia adenocarcinoma was found (89, 90), but in a register-based study an increased risk among cases of both histological types of esophageal cancer combined was found when a parent presented with esophageal cancer (91).
OCCUPATIONAL AND SOCIO-ECONOMIC FACTORS AND ESOPHAGEAL OR GASTRIC CARDIA CANCER RISK

The World Health Organization’s definition of environmental health includes both pathological effects of chemicals, radiation and some biological agents and the effects on health and well-being of the broad physical, psychological, social and esthetic environment (92). Almost all known factors influencing the risk of esophageal or gastric cardia cancer could be defined as environmental. This section presents environmental factors addressed in this thesis, factors in the work or social environment, particularly focusing on the psychosocial and chemical work environment and socio-economic factors.

Psychosocial working conditions and work-related stress

Psychosocial working conditions include the individual’s experience of the contents and organization of work, as well as of the social relations at work (93), and work-related stress (94).

Working life in most Western post-industrial economies has undergone remarkable changes over the last few decades, and the distribution of jobs continues to shift from manufacturing to services (95, 96). Increased amount of work, faster work pace, longer hours, shift work, reduced job security and temporary work are realities of the modern, often stressful, work-place (96). While the physical and chemical work environment has improved, the psychosocial work environment seems to have worsened due to these changes (95), with many European countries reporting increases of psychologically demanding work (97).

Stress has been defined as adaptation to different demands, following a pattern in three phases (alarm reaction, resistance and exhaustion) (98). All of us react to situations we perceive as threatening in a similar response pattern. The effects that are harmful to our bodies are not produced by the situation, but by our reaction to the situation, making stress a subjective experience. If our reactions to these perceived threats are continuous rather than brief, these responses may produce negative effects on our health (99).

A difference between research on work-related stress and traditional occupational health research is that psychosocial working conditions cannot be identified by direct physical or chemical measurements. Rather, theoretical models are needed to define the “toxic” components of the psychosocial work environment and quantify its effects (95). One model that has been particularly successful in dealing with these aims is the demand-control model (95), considered as one of the most influential and well-tested models in studies of health effects from psychosocial working conditions (100). The demand-control model was introduced in the late 1970s by Karasek, who later developed it together with Theorell (101, 102). Karasek’s demand-control model was a synthesis of the research traditions about demands (stress research) and lack of control (sociological research). The demand-control model’s two basic components are “psychological demands” (demands) and “control” (decision latitude). Job demands refer to work load, e.g. deadlines and work pace. The control concept has two sub dimensions, a person’s possibilities to use and develop his or her own skills (skill discretion) and a person’s possibilities to influence work activities (decision authority). Skill discretion and decision authority are highly correlated and therefore merged into the control dimension (101, 102). The demand-control model distinguishes between four types of work: 1) “High stress jobs”, with a combination of
high demands and low control, i.e. *job strain*, 2) “active jobs” with high demands and high control, 3) “low stress jobs” with low demands and high control and 4) “passive jobs”, low in both demands and control (Figure 2).

![Demand-Control Model](image)

**Figure 2.** The demand-control model.

Job strain is defined as the joint effects of the demands of the work situation and the environmental moderators of stress (i.e. control) (94). According to the model persons exposed to job strain may have an increased risk of psychological strain and disease (100). This has been tested empirically for several health outcomes, predominantly for cardiovascular disease (103, 104).

There is a general agreement that job stress results from the interaction of the individual’s own interpretations and reactions and the conditions in the work environment (96, 105). Coping is described as an important factor in the relation between stressful events and adaptational outcomes such as depression, psychological symptoms and somatic illness (106). It has been hypothesized that exposure to psychosocial factors that arouse anger may cause illness, particularly if a person is not allowed to show anger or to deal constructively with the factor that produced it (105). Two different coping styles in relation to unfair treatment or conflicts at work have been defined; open coping, primarily directed towards the aggressor, and covert (or passive) coping, directed inwards or towards others (105).

Chronic stress, such as work-related stress, has been associated with a chronic state of hyperarousal or changes in hormone levels, impairing the immune system, that in turn may have an influence on tumor development (99, 104, 107). Further, there is a general perception that psychological stress plays a role in the development of gastrointestinal disorders, such as reflux, and these associations are being investigated actively (108, 109).

Few observational studies have evaluated possible associations between the psychosocial work environment and cancer risk (104, 107). There are no studies of the significance of a stressful work environment in the etiology of esophageal or gastric cardia adenocarcinoma, but some studies are available for other malignancies. In one cohort study no association
was found between job strain and breast cancer (107, 110) and in one case-control study no consistent association between job strain and colon cancer was found (111).

**Airborne occupational exposures**

The concept of environment is often defined broadly, including all non-genetic factors such as diet, lifestyle and infectious agents. In a more specific sense, however, environmental factors include only (natural or man-made) agents encountered by humans at work or in their every day environment upon which they have no or limited personal control (112). In this strict sense the most important “environmental” exposures include outdoor and indoor air pollution and soil and drinking water contamination (112), where exposure to a chemical, physical or biological agent is usually defined as any contact between an agent in an environmental medium (e.g. air, water, soil) and the surface of the human body (e.g. skin, respiratory tract) (113). Exposure assessment is the study of the distribution and determinants of agents affecting human health (113).

Epidemiological exposure assessment of the occurrence of cancer in relation to work place exposures started after the 2nd World War, and the knowledge of occupational and environmental causes of cancer grew rapidly in the next few decades (114). Most known occupational carcinogens were identified in the 1950-70s, including for example asbestos (112). Many exposures are now less intense than in the past, since industrial hygiene has improved in industrialized countries over the last decades (114), but exposure to several important occupational carcinogens is still common, especially in developing countries (112).

Airborne particles come in many different forms, such as dusts, fumes (including solvent vapors), mists, smoke, fibers, aerosols (pesticides), smog or fog (115). Many airborne exposures occur at higher concentrations in the work environment, often in male-dominated occupations and industries (112). The esophagus may be particularly exposed to inhaled airborne particles, if these are deposited in the airway region and then swallowed (116).

Many epidemiological studies have linked esophageal cancer to employment in certain occupations and industries or to specific exposures. In some occupational groups or industries positive associations with esophageal cancer have been found, e.g. among workers in the plumbing industry (117), rubber industry workers (118-122), workers in the cement industry (123), medical X-ray workers (124), chemical manufacturing workers (125), chimney sweeps (126), plastics and composites industry workers (127), administrative and health professionals (128), dye production industry workers (129), motor vehicle industry workers (121, 130), miners (131), dry cleaning workers (132-134), restaurant workers (121, 135), seafarers (136), printing industry workers (137, 138), painting industry workers and painters (139), asphalt workers (140) and textile factory workers (141).

Specific exposures and agents that have been positively associated with esophageal cancer include metal dust (116), combustion products (142), organic solvents (143), asbestos (144), toluene (145), polynuclear aromatic hydrocarbons (146), general dust (146), silica dust (147, 148), sulphuric acid (149) and carbon black (149). Sulphuric acid has also been positively associated with gastric cardia cancer (150).
However, these studies addressed only esophageal squamous-cell carcinoma or did not distinguish between squamous-cell carcinoma and adenocarcinoma of the esophagus (116-126, 129-141, 143-149), with a majority being multiple cancer studies (117, 118, 120, 122, 125-127, 129, 130, 132, 134, 135, 137, 138, 140, 141, 143-145).

Further, a major problem with most of these studies is their lack of adjustment for potentially important confounding factors (117-120, 122, 124-130, 132, 134, 136-141, 144, 148), particularly tobacco smoking and alcohol use when studying esophageal squamous-cell carcinoma.

Thus, little is known of possible associations between occupations, industries or specific occupational exposures and risk of esophageal adenocarcinoma or gastric cardia adenocarcinoma. One of the very few studies of occupations and industries examining esophageal and gastric cardia adenocarcinoma separately, with detailed confounder data, is a large case-control study conducted in the United States (151). Here, esophageal adenocarcinoma was positively associated with employment in administrative support, health services, financial, insurance and real estate industries, while gastric cardia adenocarcinoma was positively associated with employment in transportation and certain woodworking occupations (151). Due to small number of exposed cases and lack of clear duration-response relations, the authors concluded that workplace exposures seemed to play a minor role in the etiology of these tumors (151). This study did not examine specific exposures, however.

**Socio-economic factors**

There is a gradient relationship between socio-economic status (SES) and health (152-154), with SES being associated with a wide range of diseases at all levels of decreasing SES (152). This gradient has been found in almost every developed country where it has been studied (152). Further, in many Western countries the relative inequality between different socio-economic groups regarding health is growing (155, 156), despite general access to health care.

Although there is wide agreement that people of higher social classes live healthier and longer lives than people of lower classes, there is less consensus on why this is so or which factors are most responsible (154). Widely used measures of SES at the individual level are income, education or occupation (152, 154, 157). Whatever the most important elements of SES may be, there are multiple potential pathways by which SES determines health (152, 154) and socio-economic factors are often considered as “upstream”, with SES determining later health (152). SES may influence health through social, psychological, behavioral or biological mechanisms (152). This might be due to people in upper socio-economic classes having healthier behavior or living in more privileged areas than people in lower classes, with higher exposure rates of smoking, unhealthy eating patterns, sedentary lifestyles or environmental hazards among people in lower SES groups (152, 154). Further, it is suggested that something about lower social status itself increases the risk of disease (154, 158).

Studies have reported that married adults are healthier and live longer than unmarried adults (159), an effect that is more apparent for men than for women (159-161). It has
been hypothesized that marriage increases social support and income, and reduces risky behavior and stress, all factors contributing to a better health (162).

Thus, socio-economic factors might potentially influence the risk of any cancer in many ways, but there is a lack of recent data on socio-economic factors and cancer risk (163).

Low SES and living without a partner has repeatedly been linked to an increased risk of esophageal squamous-cell carcinoma (86, 131, 164, 165). It has been suggested that, unlike esophageal squamous-cell carcinoma, esophageal adenocarcinoma may be a disease affecting persons of high SES, indicated by the predominance of esophageal squamous-cell carcinoma in developing countries (8, 166) and by the increase of esophageal adenocarcinoma mainly occurring among white men in Western populations (6, 14, 45). This suggestion is consistent with higher numbers of professionals and lower levels of area-based social deprivation seen among esophageal and gastric cardia adenocarcinoma cases in Great Britain (18, 31). However, the relation between SES and risk of esophageal or gastric cardia adenocarcinoma is much less studied than for esophageal squamous-cell carcinoma (167). In three case-control studies (69-71) and one cohort study (168) positive associations between low SES and risk of esophageal or gastric cardia adenocarcinoma were found, while in one register-based study no association was seen (167). However, two of these prior studies analyzed esophageal and gastric cardia adenocarcinoma as one combined cancer type (69, 70), and none of these studies were able to adjust for all known risk factors, including reflux or H. pylori infection.
AIMS

The overall aim of this thesis was to increase the understanding of occupational and socio-economic factors in the etiology of esophageal and gastric cardia cancers, particularly focusing on the adenocarcinomas.

The specific aims were:

**Paper I** To study if stressful psychosocial working conditions, i.e. job strain, low work pace satisfaction or covert coping, increases the risk of esophageal or gastric cardia adenocarcinoma, or esophageal squamous-cell carcinoma.

**Paper II** To investigate the association between airborne occupational exposures among male construction workers and the risk of esophageal or gastric cardia adenocarcinoma, or esophageal squamous-cell carcinoma.

**Paper III** To study the relation between socio-economic status and other socio-economic dimensions and the risk of adenocarcinoma of the esophagus or gastric cardia.

**Paper IV** To examine occupations, industries and specific airborne occupational exposures in relation to risk of esophageal or gastric cardia adenocarcinoma, or esophageal squamous-cell carcinoma.
MATERIAL AND METHODS

This thesis uses data from two different epidemiological materials. Papers I, III and IV are based on a large nationwide Swedish population-based case-control study. Paper II is based on a large cohort of Swedish construction workers. In Table 1 an overview of the materials and methods used for the four papers is presented.

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PAPER I

Study design, tumor classification, data collection

The Swedish Esophageal and Gastric Cardia Cancer Study (the SECC-study) has been described in detail previously (49, 65). This population-based case-control study encompassed the entire Swedish population younger than 80 years, born in Sweden, and living in the country during December 1, 1994 – December 31, 1997. All newly diagnosed cases of adenocarcinoma of the esophagus or gastric cardia, and half of the newly diagnosed cases of squamous-cell carcinoma of the esophagus (those born on even-numbered dates) were eligible as cases. A comprehensive organization for rapid case ascertainment including contact persons at all 195 Swedish departments of general surgery, thoracic surgery, otorhinolaryngology, oncology and pathology, as well as continuous collaboration with the six regional tumor registries in Sweden, ensured that every potential case patient throughout the country was identified soon after diagnosis. The control persons were selected randomly from the continuously updated and computerized Swedish total population register, and frequency matched according to the age (in 10 year intervals) and sex distribution of the cases of esophageal adenocarcinoma. The control sampling was distributed over the entire study period.

To reduce misclassification of the tumor site or histological type, uniform routines for prospective documentation of the tumors were developed especially for the study and used at all participating departments. The diagnosis was based on a summary of the findings at endoscopy, surgery and histopathology. Finally, one pathologist reviewed biopsy samples and surgical specimens, or both, from 97% of the cases.

All cases and controls underwent computer-aided personal interviews performed by specially trained professional interviewers from Statistics Sweden, who were instructed to treat case patients and control persons in a strictly equal manner. The majority of the case patients were interviewed within five weeks after diagnosis. The data collection took place 1995 to 1997. A computerized questionnaire with inbuilt loops and checks for inconsistencies and errors was developed specifically for the study. The average length of the interviews was 80 minutes.

Informed consent was obtained from each participant, and all regional ethics committees in Sweden approved the study.

Data on psychosocial working conditions (job strain, work pace satisfaction, coping)

The study questionnaire contained questions addressing the study participant’s psychosocial work environment during the 1970s. Included were the dimensions demands, control (i.e. decision authority and skill discretion), work pace satisfaction and coping. The measure of skill discretion was not adequate and this dimension was therefore not included in the analyses.

To measure self-reported work-related stress we used the demand-control model, previously described (101, 102). Three indices, two for the dimension decision authority and one for the dimension job demands, were used to evaluate job strain according to a previously employed method (94).
Decision authority was measured in two different ways. First, three questions describing freedom over one’s work schedule (freedom to make private telephone calls, receive private visitors or run private errands during working hours) were used to construct a variable labeled “authority specific”. Low authority specific was indicated by answering “no” to all three questions, high authority specific by answering “yes” to at least one of the questions.

Secondly, two questions measuring a more general definition of decision authority (describing influence over one’s work pace and how the work tasks should be performed) were used to construct a variable labeled “authority general”. Both variables were dichotomized into low (exposed) and high (unexposed) authority over decisions. Low authority general was indicated by answering “seldom” or ”never” to both questions, while high authority general was indicated by answering “always” or ”often” to at least one of the two questions.

Two questions regarding intensity of work pace and if the work was psychologically demanding were used to obtain a measure of demands, where the response alternatives were dichotomized into high (exposed) and low (unexposed) demands. Low demands was indicated by answering “medium work pace” or ”low work pace” to the first question and/or “seldom” or ”never” to the second question, while high demands was indicated by answering “high work pace” to the first question and “always” or ”often” to the second question.

These indices were then used to construct two different job strain variables. For one, labeled “job strain specific”, we combined high demands with low “authority specific”, dichotomized as described above. For the other, labeled “job strain general”, high demands were combined with low “authority general”. In the analyses, we compared the group with job strain to all the other groups combined (i.e. those with active jobs, low stress jobs and passive jobs).

Similar methods were used for dichotomizing the dimensions work pace satisfaction and coping, respectively. One question regarding level of satisfaction with one’s work pace was dichotomized into low (exposed) and high (unexposed) work pace satisfaction. Another question regarding how one would react if faced with unfair treatment at work or a conflict with a colleague, based on items previously used (105, 169), was dichotomized into covert (exposed) and overt (unexposed) coping. Covert coping was indicated by the response alternative “I let it pass without saying anything”, while overt coping was indicated by either of the response alternatives “I protested directly”, “I yelled at the person right away”, “I talked with the person right away” or “I spoke to the person later when I had calmed down” (105).

**Statistical analyses**

To estimate relative risks we used odds ratios (OR) and 95% confidence intervals (CI) estimated by conditional logistic regression (170). The regression models were conditional on the matching variables age and sex. Data were analyzed using the PHREG procedure in SAS (171). In multivariable models, adjustments were made for six potentially confounding factors: Reflux symptoms 5 years or more before interview (heartburn and/or regurgitation at least 50 times/year, in sum one year of study person’s life, yes/no), BMI 20 years before interview (calculated as bodyweight in kilograms divided by the square of body height in meters, in four categories based on quartiles among the controls), tobacco smoking status 2 years before interview (in three categories; never, previous,
current), alcohol use 20 years before interview (in four categories; 0, 1-5, 16-70, >70 grams of pure alcohol per week), dietary intake of fruit and vegetables 20 years before interview (frequency of intake on average per week in three categories; least, medium, highest) and educational level (in three categories, low, medium, high). We also compared relative risk estimates from models both including and excluding reflux symptoms. If reflux were in the causal path in the etiology of esophageal or gastric cardia adenocarcinoma any observed associations between work-related stress and the outcome would be reduced when controlling for reflux, and should not be included in any statistical models. Persons not answering all questions that were part of the indices were excluded from the analyses. Missing data varied between 1-9%, and were similar among cases and controls.

PAPER II

Study design, data collection

*The Swedish Construction Workers Cohort* has its origin in a nationwide occupational health service organization established jointly by the trade unions and the employer’s association within the Swedish construction industry in the late 1960s (172). The main purpose of this organization was to provide preventive health examinations to all employees within the construction industry. The cohort consists of nearly 400 000 workers who between 1971 and 1993 regularly were invited to health examinations. Although participation was voluntary, 85-90% of all eligible employees were examined at least once. The first visit defined entry into the cohort. Information on job titles and other exposures was obtained through self-administered questionnaires as well as forms completed by specially trained nurses within the health organization. After collection, the information was computerized and later stored in a database. The majority (95%) of the cohort members were males. Due to the small number of women in the cohort, and the low incidence of esophageal and gastric cardia cancers among women, we restricted the study to men.

Register linkages and cancer diagnoses

Each individual cohort member was identified by the National Registration Number (NRN), a unique ten-digit number assigned to all Swedish residents since 1947. The NRNs were used for linkage to the nationwide Swedish Cancer Register to identify all cases of esophageal or gastric cardia cancer occurring within the cohort. This register has coded esophageal cancers since 1958, and the specific site gastric cardia cancer since 1969, according to the 7th Revision of the International Classification of Diseases (ICD-7). The overall completeness of the Cancer Register has been estimated to be 98%, based on comparisons with other registers (173). The ICD-7 four-digit code for esophageal cancer is 1500, and for gastric cardia cancer 1511. The ICD-7 three-digit histopathological code for adenocarcinoma is 096, and for squamous-cell carcinoma 146. For correct censoring of persons not at risk for esophageal or gastric cardia cancer in the cohort and for complete follow-up, the cohort members were linked to the nationwide and computerized Swedish registers of Causes of Death, to ascertain date of death, and the Total Population, to identify men who had emigrated.
Assessment of airborne occupational exposure

The exposure assessment was based on job titles and has been employed in previous studies (174, 175). Only the job title at each worker's first visit was used, since the information available was insufficient for constructing lifetime occupational histories. In the mid 1970s a survey was carried out by the health organization, where the exposure patterns within over 200 occupations specific for the Swedish construction industry were studied by industrial hygienists at different work sites in different regions of Sweden (174, 175). Assessments were made for 212 job titles used to describe each individual's occupation during the period 1971-1985/86. After 1985, only 90 job titles were used. Based on the original job-exposure matrix, a similar matrix for these 90 job titles was developed by an experienced industrial hygienist. Twelve airborne agents were included in the matrix; asbestos, asphalt fumes, cement dust, concrete dust, diesel exhaust, epoxy resins, isocyanates, mineral fibers, metal fumes, organic solvents, quartz dust, and wood dust. Each of these was graded on an ordinal scale from 0 to 5, where level 3 corresponded to the Swedish threshold limit value (TLV) at the time of the study. An exposure level of 0.5 was added for diesel exhaust, including e.g. car drivers, who were considered as unexposed in the original job exposure matrix. We categorized the exposure level scales into no exposure (0), moderate exposure (0.5-1) and high exposure (2-5). We also examined combined exposure to dust and fumes. Dust exposure was defined as exposure to either asbestos, cement dust, concrete dust, mineral fibers, quartz dust or wood dust. Similarly, fume exposure was defined as exposure to either diesel exhaust, asphalt fumes or metal fumes.

Statistical analyses

After excluding all women and those men with a) a diagnosis of an esophageal or gastric cardia cancer event before their first visit, b) an unspecified or other histological type of esophageal or gastric cardia cancer, c) incorrect death dates or d) missing information on job title, smoking status or BMI, 260,052 male individuals were included in the statistical analyses. The cohort members were followed from the date of their first health examination through December 31, 2000, date of death, date of emigration, or date of a primary esophageal adenocarcinoma, gastric cardia adenocarcinoma or esophageal squamous-cell carcinoma diagnosis, whichever came first. The different cancer diagnoses were assumed to be independent events, i.e. men diagnosed with one of the three tumor types of interest were still considered to be at risk for the other two. We estimated incidence rate ratios (IRR) and 95% CIs by Cox regression (176), using calendar time as the underlying time scale. Models were estimated using the PHREG procedure in SAS (171). In multivariable models, adjustments were made for attained age (classified into 5-year age groups), calendar period at entry into the cohort (in three categories; 1971-75, 1976-80, 1981-93), tobacco smoking status at entry into the cohort (in three categories; never, previous, current) and BMI (kg/m²) at entry into the cohort (in four categories; ≤ 21.9 underweight, 22.0-24.9 normal, 25.0-29.9 overweight, ≥ 30.0 obese). Observations with missing data on any covariate included in the models were excluded from the analyses. Smoking status was not recorded 1975 to 1978, thus, all men with a first visit during these years were excluded from the multivariable models. The overall effect of each covariate was assessed by a Wald test of homogeneity across all exposure strata. This test considers all strata, rather than just pair wise comparisons to the reference group.

The study was approved by the Ethics Committee at Umeå University (Umeå, Sweden).
Study design, tumor classification, data collection
The design, tumor classification and data collection of the SECC-study is described above (paper I). The study participants were also asked to donate a venous blood sample. Serum was collected from a subset of the interviewed case and control persons. After centrifugation serum samples were stored at -70°C. Antibodies to cytotoxin-associated gene A (CagA) of *H. pylori* infection were detected with an immunoblot assay (Helicoblot 2:1; Genelabs Diagnostics, Singapore). The laboratory analyses were done blinded for case/control status.

Data on and classification of socio-economic factors (socio-economic status, education, other socio-economic dimensions)
The SECC-study’s questionnaire contained detailed information about lifetime occupational history, including questions about duration of employment, workplace and work tasks for each occupation held by the study participant for at least one year. Each study participant’s occupational history, ranging from 1-10 occupations, was classified by one reviewer, blinded for case/control status. Occupations held before 1955 were disregarded, since these were considered to be outside the relevant etiologic time window. Each occupation was coded according to the detailed 5-digit Nordic Standard Occupational Classification (NYK) (177). SES was derived from these 5-digit occupational codes, according to the Swedish socio-economic classification (SEI) (177-179). We allocated each study participant into one of the following six socio-economic classes; i) unskilled and semiskilled manual workers, ii) skilled manual workers, iii) assistant non-manual employees, iv) intermediate non-manual employees, v) employed or self-employed professionals, higher civil servants and executives (reference group), and vi) self-employed (other than professionals) and farmers. In the analyses we used each study person’s SES of longest duration after 1955, obtained from the occupational history.

Educational level was classified in accordance with the Swedish school system into three categories based on total number of years of education; low (0-9 years), medium (10-12 years), and high (13 years or more) (reference group).

Duration of living with a partner (married/cohabitant) was categorized into; < 1 year, 1-10 years, 11-30 years, and ≥ 31 years (reference group).

Place of residence was assessed both during childhood and during the 1970s (i.e. about 20 years before the interview), and categorized into rural (reference group) and urban or densely populated area.

Region of residence during childhood, and during the 1970s, respectively, was categorized into three well-defined Swedish regions; Götaland (southern Sweden), Svealand (central Sweden) (reference group), and Norrland (northern Sweden).

Number of children (including oneself) living in the household during childhood was grouped into; 1-2 children (reference group), 3-4 children, 5-6 children, and ≥ 7 children.

Statistical analyses
Conditional logistic regression was used to estimate ORs and 95% CIs, using the PHREG procedure in SAS. To study if the effects of the socio-economic factors changed after adjusting for potential “downstream factors”, we evaluated each socio-economic factor
separately in crude models as a risk factor for cancer outcome. Then we fitted multivariable models where adjustments were made for a priori known independent risk factors for the three different cancer types, categorized as described above (paper I). In the analyses of esophageal and gastric cardia adenocarcinoma adjustments were made simultaneously for reflux symptoms, BMI and tobacco smoking status. In the analyses of esophageal squamous-cell carcinoma adjustments were made for tobacco smoking status and alcohol use. The influence of dietary intake of fruit and vegetables was evaluated for each of the studied cancer types, but no effects on the estimates of the socio-economic factors were found and this variable was not included in the final models. Further, if we observed a crude effect of a socio-economic factor that was attenuated in the multivariable models, we fitted models including one potential mediating factor at the time, to see which factor explained the most of the attenuated effect. Each exposure was evaluated using the Wald test, which considers all categories of the variable and not just pair wise comparisons to the reference category. Participants with missing data on any covariate included in the models were excluded from the analyses. Missing data were few (1-4%) and similar for case and control participants. We also evaluated the influence of *H. pylori*/CagA seropositivity (yes/no) on the estimates of the socio-economic factors in the subset of participants who provided sera. The subset was thoroughly investigated for biases. Compared to the full dataset the subset was oversampled on controls, older ages and never smokers. However, the distribution of socio-economic factors was similar. These comparisons were done for all three cancer outcomes separately. Applying the fully adjusted model on the subset showed similar effect estimates for the socio-economic factors compared to the full dataset. Since age was controlled for by conditioning and smoking by adjustment in the models, a complete case analysis of the subset would be adjusted for any biases due to the skewed sampling, i.e. under the assumption of missing at random within age and smoking strata. Thus, *H. pylori*/CagA status was included as an additional covariate in the adjusted models based on the subset and its influence on the estimates of the socio-economic factors could be evaluated.

**PAPER IV**

**Study design, tumor classification, data collection**

The SECC-study’s design, tumor classification and data collection is described above (paper I).

**Classification of lifetime occupational history, occupations and industries**

As mentioned (paper III), each study participant’s occupational history, disregarding occupations before 1955, was classified using the detailed 5-digit Nordic Standard Occupational Classification (NYK) (177), and the 4-digit Swedish Standard Industrial Classification (SNI) (180). In the analyses of occupations and industries we selected the study person’s occupation or industry of longest duration (after 1955). These were aggregated into 66 occupational and 50 industry groups (2-digit classifications). A given occupation or industry of longest duration (“exposed”) was compared to all the other occupations or industries of longest duration combined (“unexposed”, reference group).
Assessment of airborne occupational exposures
We assessed cumulative occupational exposure for ten airborne agents (wood dust, metal dust, asbestos, organic solvents, pesticides, diesel exhaust, quartz dust, flour dust, combustion gases and unspecified dust). The exposure assessments were done by a senior industrial hygienist, based on manual reviews of each study participant’s self-reported occupational history, classified as described above. The reviewers had no information of case/control status. For the assessment of wood dust, metal dust, asbestos, organic solvents and pesticides we also used specific questions regarding number of yearly, monthly or weekly regular contacts with these substances. The assessment of cumulative exposure to each substance was based on the following parameters; a) probability of exposure on a scale from 0 to 2 (0=no, 1=possible, 2=probable), b) frequency of exposure (part of week/year) on a scale from 0 to 4 (0=extremely small, 1=very small, 2=minor, 3=medium, 4=major), c) intensity of exposure, considering different occupations and calendar periods, on a scale from 2 to 4 (2=low, 3=medium, 4=high) and d) duration of exposure (total number of exposed years for each relevant work period). The cumulative exposure score was calculated as the sum of a-c multiplied by d. The scores were classified into three categories; no exposure (score=0), low exposure and high exposure. For low and high exposure the score was dichotomized according to the median among all exposed.

Assessment of diesel exhaust, quartz dust, flour dust, combustion gases and unspecified dust was based on the reviews of each participant’s occupational history and was measured as duration of exposure (total number of exposed years for each relevant work period). To analyze all airborne agents on the same scale duration of exposure was multiplied by a weighted score of 6, corresponding to the midpoints of the scales of the parameters (i.e. probability=1, frequency=2 and intensity=3). The scores of cumulative exposure to quartz dust, flour dust, combustion gases and unspecified dust was summarized into one variable, labeled “unspecified particular agents”. The scores for diesel exhaust and unspecified particular agents were classified into four categories; no exposure (score=0), low exposure, medium exposure and high exposure. For low, medium and high exposure the score was categorized according to the tertiles among all exposed.

Finally, to evaluate the effect of combined exposure to many airborne agents we estimated the total exposure of particular agents. Cumulative exposure to wood dust, metal dust, asbestos, diesel exhaust, quartz dust, flour dust, combustion gases and unspecified dust was summarized into one variable, by adding the scores into a total score. This variable, labeled “total exposure of particular agents”, was classified into 5 categories; no exposure (total score=0), low exposure, medium exposure, high exposure and very high exposure. Low and medium exposure corresponded each to about 33% of all the exposed participants, high exposure corresponded to 23% of all exposed, while very high exposure corresponded to 10% of all exposed. The cut-offs were chosen as tertiles, where the upper tertile was subdivided to get an extreme group with very high exposure.

Statistical analyses
We used ORs and 95% CIs estimated from conditional logistic regression (SAS PHREG procedure). In the analyses of esophageal and gastric cardia adenocarcinoma adjustments were made for reflux symptoms, BMI and tobacco smoking status. In the analyses of esophageal squamous-cell carcinoma adjustments were made for tobacco smoking status and alcohol use. Each exposure was evaluated using the Wald test across all levels of
exposure. Participants with missing data on any covariate included in the models were excluded from the analyses. Missing data were few and fairly similarly distributed among case and control participants.
RESULTS

Study participants (papers I, III, IV)
The SECC-study included 189 patients with esophageal adenocarcinoma, 262 patients with
gastric cardia adenocarcinoma and 167 patients with esophageal squamous-cell carcinoma.
They constituted 88, 84 and 73% respectively, of all eligible case patients in the study base.
The reasons for non-participation among the cases were physical or mental disorders, early
death or unwillingness to participate. The 820 control persons constituted 73% of all who
had been primarily selected. The reasons for non-participation among the control persons
were unwillingness to participate, physical or mental disorders or that the person could not
be traced. Unwillingness was a rare reason for non-participation among case patients
(1-5%), while it was more common among the controls (19%). The majority of the
participants were men between 60 and 79 years old. 51% of the interviewed case patients
and 61% of the interviewed controls donated sera.

Study participants (paper II)
Together, the 260 052 male participants in the construction workers cohort contributed
over 5 million person-years at risk of esophageal or gastric cardia cancer during follow-up
of the cohort. 64 patients with adenocarcinoma of the esophagus, 165 patients with
adenocarcinoma of the gastric cardia and 179 patients with squamous-cell carcinoma of
the esophagus were identified. The total incidence rate per 100 000 person-years was 1.3
for esophageal adenocarcinoma, 3.3 for gastric cardia adenocarcinoma and 3.6 for
esophageal squamous-cell carcinoma. The incidence rates were higher for all esophageal
and gastric cardia cancer patients who were current smokers or had a BMI above 30 at
entry into the cohort.

Psychosocial working conditions and risk of cancer of the esophagus
and gastric cardia (paper I)
No associations between decision authority (both measures) or job demands and risk of
any of the three cancer types were observed, except for an inverse association of having
low decision authority (specific) and risk of gastric cardia adenocarcinoma (OR 0.5 [95%
CI, 0.3-0.9]).

We found no associations between job strain (both measures) and risk of esophageal
adenocarcinoma (OR 1.9 [95% CI, 0.7-5.2] for job strain general) or esophageal squamous-
cell carcinoma (OR 0.8 [95% CI, 0.2-2.4] for job strain general) (Table 2). There was a
positive association between job strain general and gastric cardia adenocarcinoma in the
model excluding reflux symptoms (OR 2.2 [95% CI, 1.0-4.8]) (Table 2).

Among persons reporting low work pace satisfaction, compared to persons reporting high,
a 3.6-fold (95% CI, 1.3-10.4) increased risk of esophageal squamous-cell carcinoma and a
2.8-fold (95% CI, 1.1-7.0) increased risk of esophageal adenocarcinoma was observed
(Table 2). The association with esophageal adenocarcinoma disappeared when adjusting for
reflux (Table 2).
Having a covert coping style, compared to persons who reacted openly when treated unfairly, was associated with moderately increased risks of both esophageal (OR 1.8 [95% CI, 1.2-2.8]) and gastric cardia adenocarcinoma (OR 1.5 [95% CI, 1.0-2.2]) (Table 2). No association was identified between coping style and risk of esophageal squamous-cell carcinoma (Table 2). The point estimates for the associations between covert coping and esophageal adenocarcinoma were marginally elevated after adjusting for reflux, while no influence of reflux on the associations between coping style and risk of gastric cardia adenocarcinoma was seen (Table 2).

Table 2. Job strain, low work pace satisfaction, covert coping and risk of esophageal or gastric cardia cancers

<table>
<thead>
<tr>
<th>Controls (n)</th>
<th>Esophageal adenocarcinoma</th>
<th>Gastric cardia adenocarcinoma</th>
<th>Esophageal squamous-cell carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>OR* (95% CI)</td>
<td>Cases</td>
</tr>
<tr>
<td>Job strain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(general)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>781</td>
<td>178</td>
<td>241</td>
</tr>
<tr>
<td>Yes</td>
<td>22</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.9b (0.7-5.2)</td>
<td>2.2b (1.0-4.8)</td>
</tr>
<tr>
<td>Work pace satisfaction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (unexposed)</td>
<td>791</td>
<td>175</td>
<td>246</td>
</tr>
<tr>
<td>Low (exposed)</td>
<td>15</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.6b (1.0-6.5)</td>
<td>1.4b (0.6-3.5)</td>
</tr>
<tr>
<td>Coping</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overt (unexposed)</td>
<td>624</td>
<td>126</td>
<td>184</td>
</tr>
<tr>
<td>Covert (exposed)</td>
<td>133</td>
<td>50</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.8b (1.2-2.8)</td>
<td>1.5b (1.0-2.2)</td>
</tr>
</tbody>
</table>

* Adjusted for the other psychosocial working conditions in the table, reflux symptoms, BMI, tobacco smoking, alcohol use, intake of fruit and vegetables and educational level.

b Adjusted for the other psychosocial working conditions in the table, BMI, tobacco smoking, alcohol use, intake of fruit and vegetables and educational level, excluding reflux symptoms.

Occupational exposures and risk of cancer of the esophagus and gastric cardia among male Swedish construction workers (paper II)

We found positive seemingly dose-response associations between exposure to both asbestos and cement dust and the risk of esophageal adenocarcinoma (Table 3). Among workers with high asbestos exposure a 4.5-fold (95% CI, 1.4-14.3) increased risk was observed (Table 3), and among men with high exposure to cement dust we found a 3.8-fold (95% CI, 1.5-9.6) increased risk of this tumor (Table 3).

High asphalt fumes exposure was positively associated with risk of gastric cardia adenocarcinoma (IRR 2.3 [95% CI, 1.0-5.3]) (Table 3), and there was evidence of a positive association between wood dust exposure and the risk of this tumor (IRR 4.8 [95% CI, 1.2-19.4]) (Table 3).
We found evidence of positive associations between moderate cement dust exposure (IRR 1.5 [95% CI, 1.0-2.3]) (Table 3) and moderate mineral fibers exposure (IRR 1.7 [95% CI, 1.0-3.0]) and risk of esophageal squamous-cell carcinoma, but no apparent dose-response relations were seen.

There were no other associations between the specific occupational exposures analyzed separately, or the combined dust or fume exposure variables, and risk of the three cancer types.

**Table 3.** Person-years and IRRs\(^a\) for esophageal or gastric cardia cancers associated with exposure to asbestos, asphalt fumes, cement dust or wood dust among male Swedish construction workers

<table>
<thead>
<tr>
<th>Asbestos exposure</th>
<th>Person-years(^b)</th>
<th>Esophageal adenocarcinoma</th>
<th>Gastric cardia adenocarcinoma</th>
<th>Esophageal squamous-cell carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>4 792 980</td>
<td>58</td>
<td>1.0 (reference)</td>
<td>161.1.0 (reference)</td>
</tr>
<tr>
<td>Moderate</td>
<td>153 120</td>
<td>3</td>
<td>1.7 (0.5-5.4)</td>
<td>3.0.6 (0.2-2.0)</td>
</tr>
<tr>
<td>High</td>
<td>78 379</td>
<td>3</td>
<td>4.5 (1.4-14.3)</td>
<td>1.0.6 (0.1-4.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P: 0.03</td>
<td>P: 0.63</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P: 0.44</td>
<td></td>
</tr>
<tr>
<td>Asphalt fumes exposure</td>
<td>4 930 026</td>
<td>64</td>
<td>1.0 (reference)</td>
<td>159.1.0 (reference)</td>
</tr>
<tr>
<td>Moderate</td>
<td>-</td>
<td></td>
<td>159.1.0 (reference)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>94 453</td>
<td>0</td>
<td>2.3 (1.0-5.3)</td>
<td>3.1.0 (0.3-3.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P: 0.04</td>
<td>P: 0.95</td>
</tr>
<tr>
<td>Cement dust exposure</td>
<td>4 599 170</td>
<td>51</td>
<td>1.0 (reference)</td>
<td>146.1.0 (reference)</td>
</tr>
<tr>
<td>No</td>
<td>4 599 170</td>
<td>51</td>
<td>1.0 (reference)</td>
<td>146.1.0 (reference)</td>
</tr>
<tr>
<td>Moderate</td>
<td>352 068</td>
<td>8</td>
<td>1.6 (0.7-3.3)</td>
<td>15.0.9 (0.5-1.5)</td>
</tr>
<tr>
<td>High</td>
<td>73 241</td>
<td>5</td>
<td>3.8 (1.5-9.6)</td>
<td>4.0.8 (0.3-3.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P: 0.01</td>
<td>P: 0.82</td>
</tr>
<tr>
<td>Wood dust exposure</td>
<td>4 701 050</td>
<td>61</td>
<td>1.0 (reference)</td>
<td>152.1.0 (reference)</td>
</tr>
<tr>
<td>No</td>
<td>4 701 050</td>
<td>61</td>
<td>1.0 (reference)</td>
<td>152.1.0 (reference)</td>
</tr>
<tr>
<td>Moderate</td>
<td>310 416</td>
<td>3</td>
<td>0.8 (0.2-2.5)</td>
<td>11.1.1 (0.6-2.0)</td>
</tr>
<tr>
<td>High</td>
<td>13 012</td>
<td>0</td>
<td>4.8 (1.2-19.4)</td>
<td>3.2.2 (0.3-15.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P: 0.92</td>
<td>P: 0.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P: 0.49</td>
<td></td>
</tr>
<tr>
<td>Total(^d)</td>
<td>5 024 479</td>
<td>64</td>
<td>165</td>
<td>179</td>
</tr>
</tbody>
</table>

\(^a\) Adjusted for attained age, calendar period at entry into cohort, tobacco smoking at entry into cohort and BMI at entry into cohort.

\(^b\) The reported person-years are the numbers for the models studying esophageal adenocarcinoma. Values are slightly different for the other two outcomes due to the different endpoints.

\(^c\) Wald test of overall effect across all occupational exposure strata.

\(^d\) Observations with missing on any covariate included in the models were excluded from the analyses.
Socio-economic factors and risk of cancer of the esophagus and gastric cardia (paper III)

In the crude model, the risk of esophageal adenocarcinoma strongly increased with decreasing levels of SES based on each individual’s occupation (Table 4). The risk was almost 4-fold increased among unskilled manual workers (OR 3.7 [95% CI, 1.7-7.7]) and self-employed (OR 3.7 [95% CI, 1.7-8.1]), compared to professionals, and more than 2-fold increased among skilled manual workers (OR 2.4 [95% CI, 1.1-5.3]) and assistant non-manual employees (OR 2.3 [95% CI, 1.0-5.3]). In the model adjusted for reflux, BMI and smoking the inverse association between SES and esophageal adenocarcinoma was attenuated, and the overall association was no longer statistically significant (Table 4). The attenuated effect was mainly explained by adjustment for BMI and reflux. The risk estimates were approximately similar in the model adjusted for H. pylori/CagA status, based on the subset who donated sera (data not shown).

A tendency of an association between low SES and an increased risk of gastric cardia adenocarcinoma was seen in the crude model, while it disappeared in the adjusted model (Table 4).

Occupational SES was inversely associated with esophageal squamous-cell carcinoma. Compared to professionals, about 2-fold increased risks were observed among all SES groups, except among skilled manual workers where an almost 4-fold increased risk was observed (OR 3.9 [95% CI, 1.7-8.9], adjusted model) (Table 4).

A moderately increased risk of esophageal adenocarcinoma among persons having less than 9 years of education compared to persons with more than 12 years of education (OR 1.8 [95% CI, 1.1-3.0]) was observed in the crude model, but this association disappeared in the adjusted model (OR 1.0 [95% CI 0.6-1.8]). To evaluate possible confounding between SES and education we included both SES and education in one model, in which low SES remained a significant risk factor while no association was seen for education (data not shown).

In the crude model, a moderately increased risk of gastric cardia adenocarcinoma was observed among persons with a low educational level, compared to persons with a high (OR 1.7 [95% CI, 1.1-2.6]), but the association was attenuated when controlling for reflux, BMI and smoking (OR 1.3 [0.8-2.1]). There was a 2-fold significantly increased risk of esophageal squamous-cell carcinoma among persons with a low educational level (OR 2.0 [95% CI, 1.1-3.6]), adjusted model.

In a model including both SES and education, the association between SES and esophageal squamous-cell carcinoma was the strongest (data not shown).

The risk of esophageal adenocarcinoma was more than 2-fold increased among persons who never or for less than one year had been married or cohabitant, compared to persons who had been living with a partner for three decades or more (Table 4). Similarly, a 2-3-fold increased risk of esophageal squamous-cell carcinoma was seen among persons who had been living with a partner for less than one year or for less than 11 years, compared to persons who had been married or cohabitant for 31 years or more (Table 4). No association was seen between duration of living with a partner and risk of gastric cardia adenocarcinoma (Table 4).

Inverse associations between living in the northern part of Sweden, compared to living in the central, and risk of esophageal adenocarcinoma were observed (data not shown).
Decreased risks of gastric cardia adenocarcinoma and esophageal squamous-cell carcinoma were observed among persons living in an urban area during childhood, compared to persons living in a rural area (data not shown).

No other associations were identified regarding the other socio-economic dimensions and risk of the three cancer types.
Table 4. Occupational SES and duration of living with a partner and risk of esophageal or gastric cardia cancers

<table>
<thead>
<tr>
<th>Socio-economic status</th>
<th>Controls (n)</th>
<th>Esophageal adenocarcinoma</th>
<th>Gastric cardia adenocarcinoma</th>
<th>Esophageal squamous-cell carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professionals</td>
<td>99</td>
<td>9</td>
<td>1.0 (reference)</td>
<td>26</td>
</tr>
<tr>
<td>Intermediate non-manual</td>
<td>134</td>
<td>17</td>
<td>1.4 (0.6-3.4)</td>
<td>33</td>
</tr>
<tr>
<td>Assistant non-manual</td>
<td>101</td>
<td>19</td>
<td>2.3 (1.0-5.3)</td>
<td>20</td>
</tr>
<tr>
<td>Skilled manual</td>
<td>158</td>
<td>37</td>
<td>2.4 (1.1-5.3)</td>
<td>55</td>
</tr>
<tr>
<td>Unskilled manual</td>
<td>190</td>
<td>59</td>
<td>3.7 (1.7-7.7)</td>
<td>73</td>
</tr>
<tr>
<td>Self-employed</td>
<td>110</td>
<td>38</td>
<td>3.7 (1.7-8.1)</td>
<td>46</td>
</tr>
</tbody>
</table>

Crudeb; 95% CI 1.0 (reference) P: 0.00

Adjustedd; 99                                1.0 (reference) 26 1.0 (reference) 24 1.8 (0.8-4.1)

Intermediate non-manual 134 1.0 (0.4-2.4)

Assistant non-manual 101 1.8 (0.7-4.6)

Skilled manual 158 1.5 (0.7-3.6)

Unskilled manual 190 2.0 (0.9-4.5)

Self-employed 110 2.4 (1.0-5.6)

P: 0.11

Duration of living with a partner

<table>
<thead>
<tr>
<th>Duration</th>
<th>Controls (n)</th>
<th>Esophageal adenocarcinoma</th>
<th>Gastric cardia adenocarcinoma</th>
<th>Esophageal squamous-cell carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 31 years</td>
<td>502</td>
<td>108</td>
<td>1.0 (reference)</td>
<td>161</td>
</tr>
<tr>
<td>11-30 years</td>
<td>219</td>
<td>41</td>
<td>1.0 (0.7-1.6)</td>
<td>66</td>
</tr>
<tr>
<td>1-10 years</td>
<td>30</td>
<td>7</td>
<td>1.2 (0.5-3.0)</td>
<td>13</td>
</tr>
<tr>
<td>&lt; 1 year</td>
<td>41</td>
<td>23</td>
<td>2.8 (1.6-4.8)</td>
<td>13</td>
</tr>
</tbody>
</table>

Crudeb; 95% CI 1.0 (reference) P: 0.00

Adjustedd; 502 1.0 (reference) 161 1.0 (reference) 101 1.0 (reference)

Intermediate non-manual 219 0.9 (0.5-1.5)

Assistant non-manual 30 1.3 (0.5-3.6)

Skilled manual 41 2.3 (1.2-4.5)

Unskilled manual 30 1.3 (0.5-3.6)

Self-employed 41 2.3 (1.2-4.5)

P: 0.06

Notes:

- Observations with missing on any covariate included in any of the models were excluded from the analyses.
- Crude ORs controlled for age and sex by matching.
- Wald test of overall effect across all exposure strata.
- ORs adjusted for reflux symptoms, BMI and tobacco smoking.
- ORs adjusted for tobacco smoking and alcohol use.
Airborne occupational exposures and risk of cancer of the esophagus and gastric cardia (paper IV)

Occupation was not associated with risk of esophageal or gastric cardia adenocarcinoma (data not shown). A non-significantly elevated risk of gastric cardia adenocarcinoma was observed among hotel and restaurant workers (OR 2.8 [95% CI, 0.9-8.5]). A 2-fold increased risk of esophageal squamous-cell carcinoma was identified among concrete and other construction workers (OR 2.2 [95% CI, 1.1-4.2]). Positive associations were also seen between health service and nursing work (OR 2.9 [95% CI, 1.0-8.8]), food and tobacco processing work (OR 5.1 [95% CI, 1.2-21.0]) and hotel and restaurant work (OR 3.9 [95% CI, 1.2-12.5]) and the risk of esophageal squamous-cell carcinoma, although the number of exposed cases were low (data not shown).

No associations were identified between employment in any specific industry and risk of esophageal adenocarcinoma, except for an inverse association between employment in the metal product industry and risk of this cancer (OR 0.3 [95% CI, 0.1-0.9]). We identified a nearly 4-fold increased risk of gastric cardia adenocarcinoma among persons in the motor vehicle industry (OR 3.9 [95% CI, 1.5-10.4]). A non-significantly elevated risk of gastric cardia adenocarcinoma (OR 2.8 [95% CI, 0.8-9.3]) and an increased risk of esophageal squamous-cell carcinoma (OR 4.9 [95% CI, 1.4-17.3]) were found among persons working in hotels or restaurants. A non-significantly elevated risk of esophageal squamous-cell carcinoma was observed among persons in the construction industry (OR 1.6 [95% CI, 0.9-2.8]).

An inverse association was observed between low metal dust exposure and risk of esophageal adenocarcinoma (OR 0.1 [95% CI, 0.0-0.7]). There were tendencies of positive associations between high exposure to pesticides and risk of both esophageal (OR 2.3 [95% CI, 0.9-5.7]) and gastric cardia adenocarcinoma (OR 2.1 [95% CI, 1.0-4.6]) (Table 5). Among workers highly exposed to “unspecified particular agents” a tendency of an increased risk of esophageal squamous-cell carcinoma was found, compared to the unexposed workers (OR 1.7 [95% CI, 1.0-2.9]) (Table 5). No other associations were identified between airborne occupational exposures and risk of esophageal or gastric cardia cancers (Table 5).
Table 5. Airborne occupational exposures and risk of esophageal or gastric cardia cancers

<table>
<thead>
<tr>
<th></th>
<th>Controls (n)</th>
<th>AEa Cases</th>
<th>ORb (95% CI)</th>
<th>PC</th>
<th>ACa Cases</th>
<th>ORb (95% CI)</th>
<th>PC</th>
<th>SCCa Cases</th>
<th>ORd (95% CI)</th>
<th>Pc</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Wood dust</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No exposure</td>
<td>732</td>
<td>166</td>
<td>1.0 (reference)</td>
<td></td>
<td>233</td>
<td>1.0 (reference)</td>
<td></td>
<td>149</td>
<td>1.0 (reference)</td>
<td></td>
</tr>
<tr>
<td>Low exposure</td>
<td>35</td>
<td>7</td>
<td>0.8 (0.3-2.0)</td>
<td></td>
<td>12</td>
<td>1.1 (0.5-2.2)</td>
<td></td>
<td>2</td>
<td>0.4 (0.1-1.9)</td>
<td></td>
</tr>
<tr>
<td>High exposure</td>
<td>32</td>
<td>8</td>
<td>0.6 (0.2-1.5)</td>
<td>0.50</td>
<td>11</td>
<td>1.0 (0.5-2.2)</td>
<td>0.97</td>
<td>9</td>
<td>2.0 (0.9-4.8)</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>Metal dust</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No exposure</td>
<td>744</td>
<td>175</td>
<td>1.0 (reference)</td>
<td></td>
<td>239</td>
<td>1.0 (reference)</td>
<td></td>
<td>151</td>
<td>1.0 (reference)</td>
<td></td>
</tr>
<tr>
<td>Low exposure</td>
<td>29</td>
<td>2</td>
<td>0.1 (0.0-0.7)</td>
<td></td>
<td>6</td>
<td>0.5 (0.2-1.3)</td>
<td></td>
<td>5</td>
<td>1.1 (0.4-3.1)</td>
<td></td>
</tr>
<tr>
<td>High exposure</td>
<td>26</td>
<td>4</td>
<td>0.4 (0.1-1.3)</td>
<td>0.02</td>
<td>11</td>
<td>1.4 (0.6-2.9)</td>
<td>0.24</td>
<td>4</td>
<td>1.2 (0.4-3.9)</td>
<td>0.92</td>
</tr>
<tr>
<td><strong>Asbestos</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No exposure</td>
<td>692</td>
<td>154</td>
<td>1.0 (reference)</td>
<td></td>
<td>219</td>
<td>1.0 (reference)</td>
<td></td>
<td>141</td>
<td>1.0 (reference)</td>
<td></td>
</tr>
<tr>
<td>Low exposure</td>
<td>56</td>
<td>13</td>
<td>0.9 (0.4-1.8)</td>
<td></td>
<td>16</td>
<td>0.7 (0.4-1.4)</td>
<td></td>
<td>10</td>
<td>0.9 (0.4-1.8)</td>
<td></td>
</tr>
<tr>
<td>High exposure</td>
<td>51</td>
<td>14</td>
<td>0.9 (0.4-1.9)</td>
<td>0.92</td>
<td>21</td>
<td>1.2 (0.7-2.0)</td>
<td>0.52</td>
<td>9</td>
<td>0.9 (0.4-1.9)</td>
<td>0.88</td>
</tr>
<tr>
<td><strong>Organic solvents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No exposure</td>
<td>664</td>
<td>145</td>
<td>1.0 (reference)</td>
<td></td>
<td>218</td>
<td>1.0 (reference)</td>
<td></td>
<td>128</td>
<td>1.0 (reference)</td>
<td></td>
</tr>
<tr>
<td>Low exposure</td>
<td>66</td>
<td>15</td>
<td>0.7 (0.4-1.5)</td>
<td></td>
<td>18</td>
<td>0.7 (0.4-1.3)</td>
<td></td>
<td>14</td>
<td>1.2 (0.6-2.3)</td>
<td></td>
</tr>
<tr>
<td>High exposure</td>
<td>69</td>
<td>21</td>
<td>1.3 (0.7-2.3)</td>
<td>0.47</td>
<td>20</td>
<td>0.8 (0.5-1.4)</td>
<td>0.44</td>
<td>18</td>
<td>1.4 (0.7-2.5)</td>
<td>0.59</td>
</tr>
<tr>
<td><strong>Pesticides</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No exposure</td>
<td>753</td>
<td>166</td>
<td>1.0 (reference)</td>
<td></td>
<td>236</td>
<td>1.0 (reference)</td>
<td></td>
<td>157</td>
<td>1.0 (reference)</td>
<td></td>
</tr>
<tr>
<td>Low exposure</td>
<td>27</td>
<td>5</td>
<td>0.8 (0.3-2.3)</td>
<td></td>
<td>7</td>
<td>0.7 (0.3-1.8)</td>
<td></td>
<td>3</td>
<td>0.8 (0.2-3.0)</td>
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</tr>
<tr>
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<td>19</td>
<td>10</td>
<td>2.3 (0.9-5.7)</td>
<td>0.18</td>
<td>13</td>
<td>2.1 (1.0-4.6)</td>
<td>0.11</td>
<td>0</td>
<td>-</td>
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<tr>
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<td>700</td>
<td>156</td>
<td>1.0 (reference)</td>
<td></td>
<td>220</td>
<td>1.0 (reference)</td>
<td></td>
<td>142</td>
<td>1.0 (reference)</td>
<td></td>
</tr>
<tr>
<td>Low exposure</td>
<td>34</td>
<td>7</td>
<td>0.7 (0.3-1.9)</td>
<td></td>
<td>9</td>
<td>0.5 (0.2-1.2)</td>
<td></td>
<td>10</td>
<td>1.7 (0.7-3.8)</td>
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<td>Medium exposure</td>
<td>34</td>
<td>6</td>
<td>0.7 (0.2-1.8)</td>
<td></td>
<td>12</td>
<td>0.9 (0.4-1.9)</td>
<td></td>
<td>6</td>
<td>0.8 (0.3-2.2)</td>
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<tr>
<td>High exposure</td>
<td>31</td>
<td>12</td>
<td>1.1 (0.5-2.5)</td>
<td>0.74</td>
<td>15</td>
<td>1.2 (0.6-2.4)</td>
<td>0.43</td>
<td>2</td>
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<td>79</td>
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<td></td>
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<tr>
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<td>1.0 (0.6-1.7)</td>
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<td>43</td>
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<td>1.3 (0.7-2.1)</td>
<td>0.52</td>
<td>40</td>
<td>1.1 (0.7-1.7)</td>
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<tr>
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<td>60</td>
<td>1.0 (reference)</td>
<td></td>
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<tr>
<td>Low exposure</td>
<td>158</td>
<td>35</td>
<td>1.0 (0.6-1.7)</td>
<td></td>
<td>43</td>
<td>0.7 (0.5-1.1)</td>
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<tr>
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<td>41</td>
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<td></td>
<td>45</td>
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<tr>
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<td>19</td>
<td>1.4 (0.7-2.6)</td>
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<td>Very high exposure</td>
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<td>0.11</td>
<td>8</td>
<td>1.8 (0.7-4.4)</td>
<td>0.29</td>
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a Observations with missing data on any covariate included in the models were excluded from the analyses.
b OR controlled for age and sex by matching and adjusted for reflux symptoms, BMI and tobacco smoking.
c Wald test of overall effect across all exposure strata.
d OR controlled for age and sex by matching and adjusted for tobacco smoking and alcohol use.
e “Unspecified particular agents”, i.e. cumulative exposure for quartz dust, flour dust, unspecified dust and combustion gases added.
f “Total exp. of particular agents”, i.e. cumulative exposure for wood dust, metal dust, asbestos and unspec. particular agents added.
DISCUSSION

METHODOLOGICAL CONSIDERATIONS

Epidemiology is defined as the distribution and determinants of disease in human populations (181). There are two types of epidemiological studies, experimental and observational. In theory, the best empirical evidence regarding disease causation should come from randomized trials in humans (114). However, it is unethical to perform experiments on humans if the exposure is harmful. Further, experimental studies are often impractical or impossible, because the incidence of most diseases is low and their latencies long, as for esophageal cancer, making the needed number of compliant volunteers unrealistically large and the study period extremely long (182). Confounding and bias distinguish experimental from observational studies.

Observational studies can be defined as descriptive or analytical. Descriptive studies answer questions like “What?”, “Where?”, “When?”, “Who?”. Analytical studies address etiological hypotheses, i.e. attempts to answer the question “Why?”. The purpose of the analytical study is to assess exposure and disease outcome in individuals, with the objective to ascertain whether the particular exposure and the particular disease are unrelated or associated (182). The relative risk (risk ratio, rate ratio) is most often used as a measure of association in analytical studies. However, an association does not necessarily indicate causation, as associations can be generated by chance, confounding and bias (182).

Study design

The two main types of epidemiological analytical studies are the cohort study and the case-control study.

A cohort study is defined as a group of designated individuals who are followed or traced over time regarding disease occurrence (181). In a prospective cohort study present exposure is documented, i.e. before start of follow-up and potential occurrence of disease. Cohort members must be at risk for the disease under study, i.e. alive and free of this disease at outset of follow-up (181). Advantages of a cohort study include the incorporation of the passage of time, allowing direct estimation of the incidence rate ratio, the prospective exposure assessment and the suitability for studying rare exposures. Drawbacks include the necessity to obtain information from large populations, as often only a minority of those who are at risk for disease actually develops the disease. This means that cohort studies are less suitable for studying rare diseases and that these studies are costly, regarding both time and money.

The case-control study aims at achieving the same goals as a cohort study, but more efficiently, using sampling. Properly carried out a case-control study provides information mirroring what could be learned from a cohort study (181). In case-control studies patients who recently have been diagnosed with the disease under study, i.e. cases, are compared with persons free of this disease, i.e. controls (114). The purpose of the control group is to estimate the distribution of the exposure in the source population, i.e. the population giving rise to the cases included in the study (the same cases that would have been included in a potential cohort study) (181). Therefore, the controls must be sampled independently.
of exposure status. If this requirement is met, and the controls are selected longitudinally throughout the course of a study (i.e. density sampling), then the odds ratio obtained in a case-control study is a proper estimation of the rate ratio (183). A case-control study is said to be population-based if the cases come from a precisely defined and identified population and the controls are sampled directly from this population (181).

Given the rarity of esophageal and gastric cardia adenocarcinoma and the long expected time period between an exposure and the detection of these tumors, the case-control design used in papers I, III and IV is well suited for studying factors potentially influencing the risk of these diseases. In our case-control study the study base was well-defined. The NRNs assigned to all Swedish residents and the existence of a nationwide and continuously updated population register permitted strict random sampling of the controls. The prospective and comprehensive case ascertainment, including contact persons at all relevant Swedish hospital departments and collaboration with the Swedish regional cancer registers, ensured that every potential case patient was identified soon after cancer diagnosis. Further, the personal interviews conducted with all participants allowed us to adjust for many potentially confounding factors. However, the retrospective data collection is a potential problem as is discussed below.

Due to the low prevalence of airborne occupational exposures, and the male predominance among patients with esophageal or gastric cardia adenocarcinoma, paper II was based on a large cohort of male Swedish construction workers. Information on exposures and potential confounders was assessed prospectively. The identification of the cohort was based on a health organization with a nearly complete coverage of individuals employed within the Swedish construction industry from 1971 to 1993 (172). Further, the follow-up and the detection of incident cancers were complete due to the high quality and nationwide coverage of the Swedish population-based registers. However, an important problem with the use of this design was that the rarity of the cancers under study resulted in a limited power, discussed below.

### Bias

Bias, or systematic errors, can be defined as a process at any stage of inference producing results that depart systematically from the true values. A study can be biased because of the way the study persons have been selected, the way the study variables are measured or some confounding factor that is not identified or appropriately adjusted for (181). Bias can be classified into three broad categories, selection bias, information bias and confounding, each discussed below.

#### Selection bias

Selection bias is a systematic error originating from the procedures used to select study persons and from factors influencing study participation (181). Selection bias is present when the association between exposure and outcome differs for those who participate and those who do not participate in a study. The existence of selection bias must be inferred, rather than observed, as the association between exposure and outcome among non-participants usually is unknown.

Non-participation that is linked to the exposure status of the studied factors is an important concern in case-control studies. Although the participation rates were high in
In our case-control study, the non-participation rate was higher among control persons (27%) than among case patients (12% for esophageal adenocarcinoma patients, 16% for gastric cardia adenocarcinoma patients, 26% for esophageal squamous-cell carcinoma patients). This was mainly due to a higher degree of unwillingness to be interviewed among controls than among cases. To examine the possibility of selection bias, 24 control persons who initially declined to participate, but later changed their minds, were analyzed separately. This group could be regarded as a sample of the non-participating controls. The analysis showed that they were strikingly similar to the other controls regarding body mass, reflux symptoms, tobacco smoking, alcohol use and educational level. This indicates that the non-participation among the controls did not introduce important selection bias.

One special form of selection bias in occupational health and mortality studies is the so-called “healthy worker effect”. This bias is introduced when workers are compared to the general population, because the general population consists of many people who cannot work because of illness. In earlier analyses based on the cohort used in paper II, the cancer incidence was lower compared to the general Swedish male population, with a standardized incidence ratio for esophagus cancer of 0.66 (172). This observation probably emanated from the cohort members being on average healthier compared to the male background population of the same age- and calendar period categories. However, this bias cannot explain our positive findings in paper II, as it is averted when workers with one job-title (exposed) are compared with workers of a different job-title (unexposed) (181), i.e. internally compared, as was done in paper II.

**Information bias**

Information bias represents systematic errors in the measurement of information on exposure or outcome. When the information collected about or from study participants is incorrect, it is often referred to as being misclassified if the variable is measured on a categorical scale, and the error leads to a person being placed in an incorrect category (181).

Misclassification can be differential or non-differential. Differential misclassification is more problematic as it can either exaggerate or underestimate an effect, whereas non-differential misclassification tends to bias an association towards the null or no-effect value, i.e. underestimates the relative risk, if an association exists (181, 184).

Misclassification of exposure/outcome is differential if such misclassification is different for those with and without the outcome/exposure (Rothman 2002). A common type of differential misclassification in case-control studies is recall bias, due to the retrospective data collection, where participants are interviewed about exposure information occurring before interview, often decades ago. Although recollection of past exposure may be problematic for both cases and controls, recall bias comes about because cases often are more able to recall than controls.

With non-differential misclassification either exposure or disease (or both) is misclassified, but the misclassification does not depend on a person’s status of the other variable. Non-differential misclassification is present in every epidemiological study to some extent (181).
The thorough tumor classification in our case-control study, described in detail previously (49), increased the validity of the outcome data in papers I, III and IV.

Recall bias may potentially have contributed to the observed associations in papers I, II and IV. However, the participants were not aware of our hypotheses of work-related stress, airborne agents or socio-economic factors in relation to these cancer types. Further, as we studied three different cancer types occurring in the same region of the body with similar symptoms, and as practically all cases were unaware of the histological type of their tumor, the absence of an association with a risk of one of the tumors could be interpreted as evidence against recall bias, e.g. the lack of a clear association between the socio-economic factors and gastric cardia adenocarcinoma. Further, esophageal or gastric cardia cancers are not generally viewed as occupational diseases and would not be expected to very much affect one’s recall of occupational history (151).

The retrospective nature of our case-control study could be a possible explanation for the low prevalence of job strain (2-5%) in paper I. Thus, when answering questions about their work situation 20 years ago the participants might have underreported job strain due to poor memory. This problem is often discussed when measuring job strain (185). However, in validity studies of retrospective data collection of psychosocial working conditions, no major differences between retrospective or prospective data collection has been found (93, 185).

Another explanation for the low prevalence of job strain in our study could be that our definition of job strain was stricter than the methods used most frequently in research on work-related stress. Usually there are scales of questions where the study person’s responses are calculated as scores, but due to time constraints only a limited number of questions could be used. Our method may have resulted in fewer individuals being classified as exposed.

However, if there exists an underestimation of exposure in our study, this exposure misclassification is likely to be non-differential, i.e. the same for cases and controls, and should influence the relative risk estimates towards the null (104, 185).

In paper II, exposure misclassification may have been introduced since we lacked information on duration of exposure, i.e. we were unable to study occupational histories since only the job title reported at the worker’s first health examination could be used. However, in a previous study based on this cohort it was found that among construction workers examined before 1986 few persons had changed their job tasks, and 96.3% had the same exposure level for both previous and current job title (186). This correlation between current and previous job indicates that the construction industry has a stable work force.

The occupational exposures included in paper II were to some extent misclassified since they were based on job titles, and not on each individual’s unique exposure level. However, the job-exposure matrix used was based on assessments of the exposure patterns within over 200 occupations specific for the Swedish construction industry. Any potential exposure misclassification occurring in this cohort is likely to be non-differential and should therefore not explain our positive findings, but only dilute the effects (174, 175). Differential misclassification was avoided by the use of cross-classification of occupation and exposure, i.e. an automatic application of exposure based
on the study participant’s job title recorded by the staff of the health organization at entry into the cohort.

A limitation in studies examining occupational and industry groups is that job titles or industries are only crude surrogates for specific occupational exposures, and variations within occupations are not considered. This exposure misclassification, if present in our analysis of occupations and industries in paper IV, is likely to be non-differential (151). Further, the main focus of paper IV was to study cumulative airborne occupational exposure, assessed by a senior industrial hygienist.

Our measures of SES, occupation, industry and airborne occupational exposures in paper III and IV were based on a detailed classification of each individual’s self-reported occupational history. Classifications of occupations and industries done by trained coders usually result in a low degree of misclassification (157).

Among the methods employed for investigating possible occupational carcinogenic exposures, i.e. the use of a) job titles, b) self-reported exposures, c) job-exposure matrices and d) expert assessments based on case-by-case evaluations of occupational histories, the expert assessment method used in paper IV is considered to be more valid and produce less misclassification than the other methods, even though it is relatively costly (187-189). However, the retrospective exposure assessment limited our ability to consider variations in the exposure levels that were not reflected in the study participant’s self-reported description of work tasks or workplaces. Potential misclassification of occupational histories or airborne exposures is likely to be non-differential, as the assessments were done blinded for case-control status (146).

Confounding
Confounding may be regarded as a mixing of effects. The properties of a confounder is commonly defined as; i) a confounder must be associated with the disease, ii) a confounder must be associated with the exposure and iii) a confounder must not be an effect of the exposure, i.e. an intermediate step in the causal pathway from exposure to disease (181).

In papers I, III and IV we were able to adjust for a large number of potential confounders in multivariable regression models, such as reflux symptoms, BMI, H. pylori/CagA status, tobacco smoking, alcohol use, dietary intake of fruit and vegetables, and all our regression models were conditional on the matching variables age and sex.

In paper II, we had information on smoking and BMI, but we lacked information on for example alcohol consumption and reflux. However, a potential association between the studied exposures and alcohol intake in this cohort is most probably small, if it exists at all. Moreover, alcohol intake is not associated with risk of esophageal or gastric cardia adenocarcinoma (62, 71, 72). An association between for example asbestos and cement dust exposure and reflux is less unlikely. This has only been studied in the extreme case of the destruction of New York City’s World Trade Center towers on September 11, 2001, where high rates of gastroesophageal reflux disease have been observed among workers with the most intense exposure to airborne pollution, including asbestos and cement dust (190).
**Chance**

Besides systematic error, discussed in the previous section, the other main type of error affecting epidemiological studies is random error or chance. Random error is variation in the data that we cannot readily explain (181). This means differences attributable to chance variation. Statistical methods are used to determine whether the observed differences are real or due to chance fluctuations. Statistical power is the probability that one can detect an effect if there really is one. It is highly influenced by the size of a study (the number of participants). The role of chance can be reflected roughly statistically by the width of confidence intervals and/or p-values.

The limited power is a problem in paper I and IV. Despite the recruitment of almost all eligible case patients throughout Sweden during a 3-year period, the low incidence of these tumors and the low exposure prevalence of job strain and individual airborne agents, respectively, limited our power to detect weak or even fairly strong associations. Further, we tested for multiple exposures and three cancer types and could have generated some positive findings due to chance only.

In paper II, chance might be the single most important source of error. Although the men in our study accumulated five million person-years at risk, the rarity of esophageal and gastric cardia cancers in Sweden, combined with the low prevalence of some of the agents under study, resulted in a limited statistical power to ascertain weak associations. Moreover, since we tested for twelve specific and two combined occupational exposures in relation to three different cancer types, we would expect two significant findings merely due to chance.

**Temporality and latency time**

An exposure must precede a disease. Thus, it is of interest to consider the compatibility of the temporal sequence of exposure and outcome with the presumed latency of the disease under study (182), to evaluate if a studied disease in any way could affect an exposure under study. This may occur if exposure and disease are measured at the same point in time (as in cross-sectional studies), or if the latency time (time between disease occurrence and diagnosis) is presumed to be long, as for esophageal and gastric cardia cancer.

In paper I, we choose to assess psychosocial working conditions 20 years before the diagnosis of cancer, as we considered this a reasonable latency period between an exposure and the fully developed invasive cancer of the esophagus or gastric cardia. In paper III and IV, we disregarded occupations before 1955 when classifying the occupational histories. Since 1955 were at least 40 years prior to diagnosis, we considered any exposure before 1955 as less relevant.

The covariates that we adjusted for in papers I, III and IV were all assessed in a time window before interview. Re reflux symptoms were assessed at least five years before interview, tobacco smoking status two years before interview and BMI, alcohol use and dietary intake 20 years before interview, respectively. However, as serum was collected at interview we choose to adjust for antibodies to CagA of *H. pylori* infection, as CagA antibodies appear to persist longer than antibodies against *H. pylori* cell-surface antigens, after *H. pylori* has been eradicated (Ye 2004).
In paper II the exposure assessment was prospective, i.e. job titles, BMI and smoking were all assessed at entry into the cohort, i.e. before start of follow-up.
INTERPRETATIONS OF THE FINDINGS
In all studies included in this thesis we analyzed adenocarcinoma of the esophagus, adenocarcinoma of the gastric cardia and squamous-cell carcinoma of the esophagus separately, as the differences in incidence rates and risk factor profiles strongly suggest that they represent biologically different malignancies (2).

Psychosocial working conditions
To our knowledge, paper I is the first study of adverse psychosocial working conditions in relation to esophageal or gastric cardia cancers. Our results revealed no associations between job strain and these tumors, except for a positive association between one job strain measure and risk of gastric cardia adenocarcinoma. Having a covert coping style when faced with unfair treatment or conflicts at work, compared to an overt, was positively associated with the risk of both esophageal and gastric cardia adenocarcinoma, while low work pace satisfaction was associated with an increased risk of both histological types of esophageal cancer. The association between low work pace satisfaction and esophageal adenocarcinoma disappeared when adjusting for reflux symptoms.

The finding of positive associations between covert coping and risk of esophageal and gastric cardia adenocarcinoma is interesting, but must be interpreted cautiously as this is the first study to present such data. In a Swedish cross-sectional study a positive association between covert coping and high blood pressure was found in men, but not in women (191). Further, in a case-control study in the United States, hypertension was associated with a 2-fold increased risk of esophageal and gastric cardia adenocarcinoma combined (70). Antihypertensive drugs, relaxing the lower esophageal sphincter, might explain the increased risk of these cancers associated with hypertension. It has been shown that long-term use of medications relaxing the lower esophageal sphincter may increase the risk of esophageal adenocarcinoma (56). A sphincter relaxing effect could be a mechanism explaining also the associations between covert coping and esophageal or gastric cardia adenocarcinoma. Further, other psychosocial factors, such as social support at work, might influence these associations. Unfortunately, we were unable to study social support at work in our study.

The positive associations observed between low work pace satisfaction and risk of esophageal adenocarcinoma and gastric cardia adenocarcinoma could be due to stress responses impairing the immune system, with a subsequently increased cancer risk (99, 104, 107). Further, as the association with esophageal adenocarcinoma disappeared when reflux symptoms were included in the model, one explanation could be an increased occurrence of reflux secondary to stress responses (108).

In contrast to studies of other diseases, we found an inverse association between low decision authority (specific authority) and gastric cardia adenocarcinoma. A negative change in decision authority, in men, has been reported as an important risk factor for myocardial infarction (192). One explanation for our finding could be that persons reporting low decision authority experience these conditions as comfortable, not stressful.

The risk estimates for esophageal and gastric cardia adenocarcinoma were different for the two different measures of job strain, i.e. job strain including authority specific and job strain including authority general, and the only significant association regarding job strain
was seen between job strain general and gastric cardia adenocarcinoma. The ORs for esophageal and gastric cardia adenocarcinoma, unadjusted for reflux symptoms, was 0.5 and 0.4 for job strain specific, compared to 1.9 and 2.2 for job strain general, respectively. Authority specific concerns freedom over work schedule, while authority general concerns influence over work pace and how the work should be performed, perhaps more important aspects of decision authority.

In our study the assessment of job strain was based on self-reports regarding the study participant’s work situation during the 1970s, and job strain might have been underestimated. Thus, it would be of interest to link the occupational codes classified in our study to the job-exposure matrix regarding psychosocial working conditions developed by Johnson et al (Johnson 1993). This matrix is also based on self-reported questionnaire data, but provides a less strict method of assessing job strain than the one used in paper I, and a possibility to compare the person’s own information regarding psychosocial working conditions with all occupation(s) the person has had from the 1950s and onwards.

The associations observed in paper I could be due to chance, as we tested for many exposures and three cancer types. Further studies are needed before any firm conclusions can be drawn.

**Airborne occupational exposures**

There are several potential risk exposures that only exist in male-dominated occupations, due to the gender segregated Swedish labor market, and this could be of importance considering the strong male-predominance among patients with esophageal or gastric cardia adenocarcinoma. Therefore, we hypothesized that airborne particles in male-dominated occupations could be captured in the airways and then swallowed to act as carcinogens directly on the esophageal or cardia mucosa. To test these hypotheses we used two different study designs, two different exposure assessment methods and two different study populations.

Paper II is, to our knowledge, the first prospective study of esophageal adenocarcinoma and gastric cardia adenocarcinoma analyzed separately, investigating specific airborne agents. Exposures were assessed through a job-exposure matrix based on over 200 industry specific job titles, and information about tobacco smoking and body mass was collected. Here, we observed, although with limited precision, positive associations between exposure to asbestos and cement dust and risk of esophageal adenocarcinoma, and between exposure to asphalt fumes and wood dust and risk of gastric cardia adenocarcinoma. Evidence of positive associations was seen between exposure to cement dust and mineral fibers and risk of esophageal squamous-cell carcinoma.

Paper IV is the first study to investigate these tumors separately in relation to detailed airborne occupational exposure data, assessed by an expert rating method based on each study participant’s occupational history, and including all established risk factors for esophageal or gastric cardia adenocarcinoma, and esophageal squamous-cell carcinoma. Our results suggest no major influence of airborne occupational exposures in the etiology of esophageal or gastric cardia adenocarcinoma. However, there were indications of increased risks of both esophageal and gastric cardia adenocarcinoma among persons
highly exposed to pesticides. A positive association between employment in the motor vehicle industry and risk of gastric cardia adenocarcinoma was observed. Increased risks of esophageal squamous-cell carcinoma were identified among concrete and construction workers, hotel and restaurant workers, food and tobacco processing workers and among persons with health service and nursing work, and a high total number of inhaled particles seemed to increase the risk of this tumor.

The results regarding esophageal adenocarcinoma and asbestos in paper II and paper IV are inconsistent. We found no association in paper IV, while a positive seemingly dose-response association was observed in paper II. A major advantage regarding the exposure assessment in paper IV is our reviews of each study participant’s occupational history and the expert assessment done by a senior industrial hygienist, where asbestos and other exposures were carefully evaluated. In paper II we could only use the study participant’s job title at entry into the cohort and lacked information regarding duration of exposure, which should dilute any true association. Workers within the Swedish construction industry were all more or less exposed to asbestos before it was banned in Sweden 1976. They form the largest group of asbestos-exposed people in Sweden. This means that asbestos might have been underestimated in paper II. However, the findings in paper II have a limited precision. Thus, chance is a possible explanation for the positive association between asbestos exposure and esophageal adenocarcinoma. Another explanation is that the case-control study used in paper IV is population-based and a wide variety of occupations were included, almost none of them being insulators, and this group have the highest exposure of asbestos in the construction workers cohort. Further, asbestos, as well as asphalt fumes and wood dust, have known carcinogenic effects in the organs where they have been deposited (112, 193). Therefore, no firm conclusions can be made until additional research is available.

The finding of a positive, though imprecise, association between wood dust exposure and gastric cardia adenocarcinoma was not confirmed in paper IV. However, in a previous study using occupational and industry groups, based on occupational histories, a positive association between this cancer and wood working occupations was suggested (151). Future research is required to establish possible associations between wood dust and asphalt fumes and the risk of this tumor.

In paper II, evidence of a positive association between cement dust exposure and risk of esophageal squamous-cell carcinoma was observed, and in paper IV we observed an increased risk of this tumor among concrete and construction workers, as well as among persons highly exposed to particular agents. Silica dust (147, 148, 194) and general dust (146) have been positively associated with the risk of esophageal squamous-cell carcinoma. This suggests that occupational exposure to dust might be associated with an increased risk of esophageal squamous-cell carcinoma.

In paper IV, possible positive associations between high exposure to pesticides and risk of esophageal and gastric cardia adenocarcinoma were observed. In one study of agricultural pesticide use and risk of esophageal and gastric adenocarcinoma analyzed separately, no associations were found (195). Pesticides are used in agriculture, but no associations between agricultural work and risk of these tumors were identified in our study. However, our assessment of each study participant’s individual pesticide exposure included all
occupational exposure to pesticides, not only agricultural work. Moreover, about half of the agricultural workers in our study did not report any use of pesticides and were therefore considered unexposed, confirming the relatively low use of pesticides among farmers in Sweden. Our results might be explained by a threshold effect, with only a minority of workers exposed to pesticides exceeding this threshold. However, pesticides have a large toxicological diversity and detailed pesticides information was not collected in our case-control study, and we could not consider type of pesticides. These findings warrant cautious interpretation. Additional research in studies where high frequency of pesticides occur should explore in more detail the relation between exposure to pesticides and risk of esophageal or gastric cardia adenocarcinoma.

The elevated risks of esophageal squamous-cell carcinoma and gastric cardia adenocarcinoma that were observed among hotel and restaurant workers might be due to residual confounding by smoking or alcohol consumption. Another explanation could be passive smoking, as workers in restaurant and bars are highly exposed to environmental tobacco smoke (196).

The overall finding in paper IV of a minor role of workplace exposures in relation to esophageal or gastric cardia adenocarcinoma is consistent with a previous study examining occupational and industry groups, but not specific exposures (151). Our results suggest that airborne occupational exposures are of no major importance in the etiology of esophageal and gastric cardia adenocarcinoma.

Socio-economic factors
To our knowledge, paper IV is the first study of esophageal and gastric cardia adenocarcinoma in relation to SES derived from occupational histories, with the ability to adjust for all known risk factors. Our results suggest that low SES based on occupation and life without a partner is associated with strongly increased risks of adenocarcinoma of the esophagus. Similar patterns were observed for esophageal squamous-cell carcinoma, while no such associations were found for gastric cardia adenocarcinoma.

We observed a stronger relation between SES based on occupation compared to education and risk of esophageal adenocarcinoma. Occupation could therefore be a more informative measure of SES than education in relation to this tumor, since individual circumstances can change importantly after education is completed (168), and since SES derived from occupation usually lasts longer and comes after the years in school, making the time-window for cancer development more relevant. Moreover, mortality seems to be more strongly associated with adulthood social class, i.e. occupational SES, than education (197).

The association between occupational SES and esophageal adenocarcinoma was only partly explained by reflux, body mass and smoking, and not explained by *H. pylori* infection or dietary intake of fruit or vegetables. Therefore, there are probably other factors more common in low SES groups that might explain this association, including social, psychological, behavioral or biological factors not yet identified. Two explanations suggested for an association between occupational SES and disease are differences between occupational groups regarding behavioral and living conditions, and differences
regarding occupational risk factors (100). As suggested in paper II and IV airborne occupational exposures do not seem to be such risk factors.

An inverse association between SES and esophageal squamous-cell carcinoma has been seen in many studies (71, 86, 164). Our study confirms that low SES may act independently of the main risk factors, i.e. tobacco and alcohol use. Therefore, the underlying or mediating exposures or mechanisms are yet to be identified.

The inverse association between SES and esophageal adenocarcinoma is consistent with previous studies (69-71, 168) conducted in the United States and the Netherlands. However, two of these studies (69, 70) did not analyze esophageal and gastric cardia adenocarcinoma separately, and none of these studies were able to adjust for all known risk factors, including reflux and \textit{H. pylori} infection. However, the similarities with these studies and ours, despite large differences in health care and welfare systems between the United States and Sweden, are interesting. Even in a country like Sweden with equal access to health care low SES is strongly related to an increased risk of esophageal adenocarcinoma.

The observed increased risks of esophageal adenocarcinoma and squamous-cell carcinoma among persons who never, or for shorter periods only, had been married or cohabitant, compared to persons who had been living with a partner for decades, has previously only been reported regarding esophageal squamous-cell carcinoma (86, 165). Considering the unexplained male predominance among patients with esophageal adenocarcinoma this finding might be particularly interesting. Adjustment for the established risk factors did not attenuate the risk estimates. Further studies exploring potential influence of social support and other factors are warranted.

Although esophageal adenocarcinoma is a disease mainly affecting white men in affluent Western societies, the gradient relationship observed regarding SES and esophageal adenocarcinoma is consistent with the constant SES gradient seen for a wide range of diseases in this part of the world (152). Our results suggest that low SES might be an independent risk factor for this tumor, acting separately from established risk factors. It is important to find the yet unidentified mechanisms that might explain this strong association, and explore if exposures more common within low SES groups may, at least partly, contribute to the rising incidence of esophageal adenocarcinoma.
CONCLUSIONS

Work-related stress does not seem to be associated with an increased risk of esophageal or gastric cardia adenocarcinoma, or esophageal squamous-cell carcinoma. However, the interplay between a stressful work environment and the individual's own responses to it, indicated by covert coping or low work pace satisfaction, may be associated with moderately increased risks of these cancers. These results need to be confirmed in other studies until firm conclusions can be drawn.

Airborne occupational exposures do not seem to be of major importance in the etiology of esophageal or gastric cardia adenocarcinoma. However, we observed, although with limited precision, strong positive associations between exposure to asbestos and cement dust and risk of esophageal adenocarcinoma, and moderate positive associations between exposure to asphalt fumes and wood dust and risk of gastric cardia adenocarcinoma. Further, there were indications of positive associations between high pesticides exposure and risk of both esophageal and gastric cardia adenocarcinoma. To make any firm conclusions regarding these possible associations, additional research is needed.

High exposure to inhaled particles may be positively associated with esophageal squamous-cell carcinoma.

Low socio-economic status and life without a partner may strongly increase the risk of esophageal adenocarcinoma and esophageal squamous-cell carcinoma, associations not fully explained by established risk factors. Thus, it is of importance to find possible preventable underlying or mediating mechanisms.
SVENSK SAMMANFATTNING

Bakgrund

Delarbete I
I delarbete I undersökte vi om stressiga psykosociala arbetsvillkor i form av ”job strain” (höga krav och låg kontroll i arbetet), passiv coping samt låg tillfredsställelse med arbetstaten ökar risken för adenocarcinom i esofagus och cardia. Delarbetet baseras på en svensk, rikstäckande, populationsbaserad fall-kontrollstudie där alla relevanta sjukhuskliniker i Sverige deltog. Studien omfattade hela Sveriges befolkning yngre än 80 år, födda i Sverige och boende i landet 1995-1997. Alla nydiagnostiserade patienter med adenocarcinom i esofagus och cardia, och hälften av de patienter som insjuknade med skivepitelcancer, var valbara som fall. Kontrollpersoner valdes slumpvis från det svenska totala befolkningsregistret efter frekvensmatchning avseende ålder och kön. Alla fall- och kontrollpersoner genomgick datorstödda personliga intervjuer. I studien deltog 189 patienter med adenocarcinom i esofagus, 262 patienter med adenocarcinom i cardia, 167 patienter med skivepitelcancer i esofagus samt 820 kontrollpersoner. Med multivariabel conditional logistisk regression beräknades relativ risk i form av odds ratios (OR), med 95% konfidensintervall (KI), justerade för potentiella confounders. Vi fann inga samband mellan två olika mått av job strain och de tre tumörtyperna, förutom avseende ett mått som gav en ökad risk för adenocarcinom i cardia (OR 2.2 [95% KI 1.0-4.8]). Vi fann en association mellan passiv coping, jämfört med aktiv, och en måttligt ökad risk för både adenocarcinom i esofagus (1.8 [95% KI 1.2-2.8]) och cardia (OR 1.5 [95% KI 1.0-2.3]). Bland personer som rapporterade låg arbetstakststillfredsställelse identifierades en nära 4-faldigt ökad risk för skivepitelcancer i esofagus (OR 3.8 [95% KI 1.3-11.0]), och en nästan 3-faldigt ökad risk för adenocarcinom i esofagus (OR 2.8 [95% KI 1.1-7.0]). Vår slutsats är att arbetsrelaterad stress inte förefaller öka risken för adenocarcinom i esofagus och cardia. Samspelet mellan en stressig arbetsmiljö och individens reaktioner kan dock vara associerat med en måttligt ökad risk för dessa cancerformer.

Delarbete II
En möjlig förklaring till könsskillnaderna bland patienter med adenocarcinom i esofagus och cardia kan vara att vissa yrkesexponeringar enbart förekommer i mansdominerade branscher. Vi undersökte därför sambandet mellan luftburna yrkesexponeringar som förekommer i bygg-branschen och risken för esofagus- och cardiacancer. I detta delarbete
använde vi prospektiva data från en stor kohort bestående av svenska byggnadsarbetare. Totalt följes 260 052 män under åren 1971-2000 avseende utvecklingen av adenocarcinom respektive skivepitelcancer i esofagus samt adenocarcinom i cardia genom länkning till de svenska cancer-, dödsorsaks- samt totala befolkningsregistren. Exponeringsbedömningar av 200 yrketitlar utfördes av yrkeshygieniker och 12 luftburna yrkesexponeringar analyserades. Med multivariat Coxregression beräknades incidence rate ratios (IRR) och 95% KI, justerade för uppnädd ålder, kalenderperiod, rökning och kroppsmassa. Vi fann posativa samband mellan hög asbest- (IRR 4.5 [95% KI 1.4-14.3]) och cementdammsexponering (IRR 3.8 [95% KI 1.5-9.6]) och risk för adenocarcinom i esofagus. Vi identifierade även positiva associationer mellan exponering för asfaltrök (IRR 2.3 [95% KI 1.0-5.3]) och trädamm (IRR 4.8 [95% KI 1.2-19.4]) och risk för cardiacancer. Vi fann inga övertygande associationer avseende skivepitelcancer i esofagus. Slutsatsen är att asbest- och cementdammsexponering kan vara riskfaktorer för adenocarcinom i esofagus, och asfaltrök- och trädammsexponering kan öka risken för cardiacancer. Dessa associationer kan dock inte förklara de stora könsskillnaderna bland patienter med dessa tumörtyper.

Delarbete III
Anledningen till den i västvärlden snabbt ökande incidensen av adenocarcinom i esofagus är okänd. Medan låg socioekonomisk status (SES) ökar risken för skivepitelcancer i esofagus är sambandet avseende adenocarcinom oklart. Liksom i delarbete I använde vi den svenska populationsbaserade fall-kontrollstudien av riskfaktorer för esofagus- och cardiacancer. Vår klassificering av SES baserades på varje studiepersons yrkeshistoria. Relativ risk i form av odds ratios (OR) och 95% KI beräknades genom conditional logistisk regressionsanalys, i modeller enbart kontrollerade för kön och ålder genom matchning, och i multivariabla modeller. Risken för både adenocarcinom och skivepitelcancer i esofagus ökade med minskande SES; icke facklärda arbetare hade en 3.7-faldigt (95% KI 1.7-7.7) respektive 2.1-faldigt (95% KI 1.0-4.7) ökad risk för dessa tumörer, jämfört med ålders- och könsmatchade högre tjänstemän. Justering för refluxsymptom, övervikt och tobaksrökning reducerade överrisken för adenocarcinom i esofagus, medan resulterna inte påverkades efter justering för *Helicobacter pylori*-infektion bland ett urval av de intervjuade deltagarna. Att leva utan partner var associerat med en 2-faldigt ökad risk för bågge histologiska typerna av esofaguscancer, samband som kvarstod även efter multipla justeringar. Vår slutsats är att både adenocarcinom och skivepitelcancer i esofagus hör samman med låg socioekonomisk status och singelliv. Dessa associationer kan enbart delvis förklaras av etablerade riskfaktorer och intensifierad forskning är motiverad.

Delarbete IV
Orsakerna till incidensökningen och den manliga dominansen bland patienter med adenocarcinom i esofagus och cardia är fortfarande okända och vi undersökte om luftburna yrkesexponeringar i mansdominerade branscher ökar risken för dessa cancerformer. Vi använde vår rikstäckande, svenska populationsbaserade fall-kontrollstudie (se delarbete I). Baserat på varje studiepersons yrkeshistoria bedömde vi kumulativ luftburen yrkesexponering för tio ämnen genom en additiv modell som inkluderade konfidents, intensitet och frekvens. Dessa ämnen analyserades både var för sig och sammanslaget. Dessutom analyserades yrken och branscher med lägst varaktighet. Vi använde conditional logistisk regression för att beräkna relativ risk (OR), med 95% KI,
justerade för potentiella confounders. Vi fann tendenser till positiva associationer mellan hög bekämpningsmedelsexponering och risk för adenocarcinom i esofagus (OR 2.3 [95% KI 0.9-5.7]) och cardia (OR 2.1 [95% KI 1.0-4.6]). En tendens till en positiv associations identifierades mellan hög totalexponering av partikulära ämnen och skivepitelcancer i esofagus (OR 1.7 [95% KI 1.0-2.9]). Vi fann en 2.2-faldigt (95% KI 1.1-4.2) ökad risk för skivepitelcancer i esofagus bland byggnadsarbetare och en 3.9-faldigt (95% KI 1.5-10.4) ökad risk för adenocarcinom i cardia bland personer inom motorfordonsindustrin. Bland hotell- och restaurangarbetare identifierades en ökad risk för skivepitelcancer i esofagus och en tendens till en ökad risk för adenocarcinom i cardia. Vi fann inga andra övertygande associationer mellan luftburen yrkesexponering, yrke eller bransch och de tre cancerformerna. Vår slutsats är att luftburen yrkesexponering inte förefaller ha någon stor betydelse i etiologin till adenocarcinom i esofagus och cardia.
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