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Epidemiological Studies of the Etiology of Pancreatic Cancer

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To my son Boqian

ABSTRACT

Pancreatic cancer is one of the most lethal human cancers with less than 5% of patients surviving 5 years. Despite an urgent need for primary prevention, little is known about the etiology of this cancer. This thesis was aimed at increasing our understanding of the etiology of pancreatic cancer with regard to lifestyle and infectious agents. We first analyzed the secular trends of pancreatic cancer in Sweden and then focused on studying risk factors.

Firstly, we retrieved all incident cases (46,257) of pancreatic cancer from the Swedish Cancer Register and all mortality cases (53,686) from the Causes of Death Register between 1960 and 2003, to investigate the underlying temporal trends of pancreatic cancer by both incidence and mortality rates. A similar pattern of trends was observed irrespective of whether incidence or mortality was used. The age-standardized rates of pancreatic cancer increased during the first decade and then peaked for both sexes (the male peak occurred in the early 1970s and the female peak in the 1980s) followed by a steady decline in both groups. The close agreement between the incidence and mortality and the gender disparity suggest a true decline in pancreatic cancer incidence in recent years in Sweden, and gender-specific trends in exposure to environmental risk factors.

Secondly, we used the large Swedish Construction Workers Cohort to investigate the association between Swedish moist snuff (snus) use and the risk of pancreatic cancer. Overall, 279,897 men who were construction workers in 1978-92 were included and followed up until the end of 2004. In order to better control the strong confounding effect of smoking, we mainly focused on 83 pancreatic cancer cases in the 125,576 never-smokers and assessed the pure effect of snus use using Cox proportional hazards regression. The main finding in this study is that snus users who had never smoked had a doubled risk (95% confidence interval [CI]: 1.2-3.3) of pancreatic cancer compared with men who never used any tobacco, with some evidence of a dose-risk association. Thus, despite its comparably low levels of tobacco-specific nitrosamines, the Swedish snus may not be an entirely safe product as an alternative to cigarette smoking.

Thirdly, we took advantage of the large prospective Women's Health Initiative in the United States with measured anthropometric factors and detailed potential confounders, to examine the role of obesity, especially central obesity (measured as waist-to-hip ratio [WHR]) on the risk of pancreatic cancer. Again, Cox proportional hazards regression models were used to estimate relative risk. In total, 251 incident cases of pancreatic cancer were identified over an average 7.7 years of follow-up among 138,503 postmenopausal women. Among all tested anthropometric variables, only WHR was significantly associated with the risk of pancreatic cancer. The risk of pancreatic cancer increased 27% (95% CI: 7%-50%) per 0.1 increase of WHR. In addition, we noted that women who were current smokers with the highest WHR had a 3.7-fold (95% CI: 2.1-6.4) elevated risk of pancreatic cancer compared with never smoking women with the lowest WHR (p for interaction = 0.03). Findings from this study suggest that the WHR may be a better predictor for the disease risk in postmenopausal women.

Finally, we used two types of peptic ulcer (gastric and duodenal) to test two proposed models (increased intragastric N-nitrosamine formation or hyperchlohydria) for the observed link between *Helicobacter pylori* (*H. pylori*) infection and pancreatic cancer, since gastric ulcer is primarily associated with corpus colonization of *H. pylori*, atrophic gastritis and formation of N-nitrosamines, while duodenal ulcer is usually related to antral colonization and hyperacidity release. We retrieved 88,338 patients hospitalized for gastric ulcer and 70,516 patients for duodenal ulcer from the Swedish Inpatient Register between 1965 and 2003. Following operation for peptic ulcer, 14,887 patients who underwent gastric resection and 8,205 with vagotomy were analyzed separately. Standardized incidence ratios (SIRs) were used to estimate the risk for pancreatic caner. During 3-38 years of follow-up, we observed a small excess risk (SIR=1.2, 95% CI 1.1-1.4) for pancreatic cancer among unoperated gastric ulcer patients comparing to the Swedish general population, and the risk increased with increasing duration of follow-up (p for trend = 0.03). Patients who underwent gastric resection had 50% (95% CI: 10%-110%) excess risk of pancreatic cancer comparing to the Swedish general population. The risk increased with time since surgery, reaching 2.1-fold (95% CI 1.4-3.1) 20 years after gastric resection. Unoperated duodenal ulcer was not associated with pancreatic cancer risk, nor was vagotomy. Findings from this study lend indirect support to the nitrosamine hypothesis, but not to the hyperacidity hypothesis, in the etiology of pancreatic cancer.

LIST OF PUBLICATIONS

I. Luo J, Adami HO, Reilly M, Ekbom A, Nordenvall C, Ye W. Interpreting trends of pancreatic cancer incidence and mortality: a nation-wide study in Sweden (1960 - 2003). ***Cancer Causes Control*** *2007; Oct 18; [Epub ahead of print]*

II. Luo J, Ye W, Zendehdel K, Adami J, Adami H-O, Boffetta P, Nyren, O. Oral use of Swedish moist snuff (snus) and risk of cancer of the mouth, lung and pancreas in male construction workers: a retrospective cohort study. ***Lancet*** *2007; 369; 2015-20*

III. Luo J, Margolis KL, Adami HO, Lacroiz A, Ye W. Obesity and risk of pancreatic cancer among postmenopausal women: the Women's Health Initiative (United States). ***Submitted***

IV. Luo J, Nordenvall C, Nyren O, Adami HO, Permert J, and Ye W. The risk of pancreatic cancer in patients with gastric or duodenal ulcer disease. ***Int J Cancer*** *2006;120:368-72*

CONTENTS

LIST OF ABBREVIATIONS

IARC	International Agency for Research on Cancer
BMI	Body mass index
WHR	Waist-to-hip ratio
H. pylori	*Helicobacter pylori*
PanIN	Pancreatic intraepithelial neoplasia
NSAIDs	Non-steroidal anti-inflammatory drugs
PAH	Polycyclic aromatic hydrocarbons
ICD	International Classification of Diseases
WHI	Women's Health Initiative
SEER	Surveillance Epidemiology and End Results
AIC	Akaike information criterion
RR	Relative risk
CI	Confidence interval
SIR	Standardized incidence ratio
DCO	Death certificate only

1 INTRODUCTION

Pancreatic cancer is one of the most lethal human cancers with less than 5% of patients can survive 5 years. The survival rates have not improved substantially over the past few decades due to the lack of significant medical advancements in its early detection or treatment (1-3). Although primary prevention is urgently needed for this deadly disease, little is known about its etiology. Cigarette smoking is the only established risk factor for pancreatic cancer with relative risk about two (4). Inherited factors account for 5-10% of all cases (5). Other consistently reported risk factors include chronic pancreatitis (6, 7) and type II diabetes (8).

As with nearly all other types of cancer, pancreatic cancer has an uneven geographic distribution. The highest incidences of pancreatic cancer are found in developed countries and lower rates in developing countries. Part of the international variation in incidence rates may be due to differences in detection of this cancer and completeness of case ascertainment (9). The incidences of pancreatic cancer increased for several decades early in the past century, but have leveled off in most developed countries where the rates are already high, whereas the rates continued to increase in countries that had relatively low rates 4 decades ago (10). The substantial international variations in rates of pancreatic cancer and its different patterns of time trends suggest that environmental factors are likely to play a major role in the development of the disease.

Pancreatic tumors can arise from both parts (exocrine and endocrine) of the pancreas, but those formed by the exocrine pancreas are much more common, and account for about 95% of all pancreatic cancers (11). This thesis has only focused on exocrine pancreatic tumors. The objectives of the thesis are to first analyze the secular trend of pancreatic cancer; and then focus on studying different risk factors in order to shed light on the etiology of this deadly disease.

2 BACKGROUND

2.1 CLINICAL ASPECTS OF PANCREATIC CANCER

2.1.1 Symptoms

Pancreatic cancer has an insidious onset. Most patients with pancreatic cancer are initially seen with the development of jaundice, caused by blockage of the common bile duct. Other symptoms may include weight loss, fatigue, abdominal pain, newly diagnosed diabetes mellitus and nausea (12, 13). Those presenting symptoms are non-specific and usually occur late in the course of the disease. As a result, pancreatic cancer is usually diagnosed at an advanced stage, when a curative resection is no longer possible.

2.1.2 Diagnosis

Until recently, because of its deep location, diagnosis of pancreatic cancer has always been a challenge. There are now a number of techniques that allow imaging of the pancreas, including endoscopic ultrasound (EUS), computed tomography (CT), contrast-enhanced multi-detector row helical CT (MDR-CT), endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance imaging (MRI), and fine-needle aspiration biopsy guided by ultrasound (14, 15), and these modalities have improved significantly in the last 5 years (16). However, no individual imaging technique has yet achieved sufficient accuracy to precisely assess tumour resectability in pancreatic cancer. Normally, combinations of different imaging modalities are employed in the preoperative staging of patients with suspected pancreatic carcinoma (17).

In addition, although many biochemical markers have been examined in relation to pancreatic cancer, none is definitive for pre-operative diagnosis. CA 19-9 is the most extensively evaluated marker with a median sensitivity of CA 19-9 for diagnosis of 79% and median specificity of 82% (18). Several studies (19, 20) have examined the role of CA 19-9 as a population screening tool, but it is ineffective in asymptomatic patients.

2.1.3 Prognosis

Because screening tests are not available for early detection and no specific symptoms are apparent before it is detected in advanced stages, pancreatic cancer has the lowest survival rate of any major cancers (21). Due to the high fatality rates, pancreatic cancer incidence rates are almost equal to the mortality rates. The median duration of survival after diagnosis is less than 6 months (12), and less than 5% of patients survive 5 years (2, 3, 21).

In addition, the survival rates have not improved substantially over the past few decades (2), although some new imaging techniques have been introduced since the early 1980s. The only potential cure for pancreatic cancer is operation, sometimes combined with pre-, peri- or post-operative radiotherapy and/or adjuvant chemotherapy. However, only a small fraction, about 15-20%, of all patients are resectable at the time of diagnosis when their pancreatic cancer is still localized and within reach for radical surgical removal (1, 13).

2.2 DESCRIPTIVE EPIDEMIOLOGY OF PANCREATIC CANCER

2.2.1 Geographic variation of incidence/mortality

Pancreatic cancer causes more than 200,000 deaths per year, ranking the eighth leading cause of cancer death in both sexes combined globally, a relative position higher than for incidence (thirteenth) because of the poor prognosis (9).

The majority of pancreatic cancer cases (61%) occurs in developed countries, where age-adjusted incidence and mortality rates to World standard population (proposed by Segi in 1960) are between 7 and 9 per 100,000 in men and 4.5 and 6 per 100,000 in women, with lower rates in developing countries (9). In the United States, pancreatic cancer is the fourth leading cause of cancer death, while it is the sixth in the European Union (22).

2.2.2 Gender and age distribution

On a worldwide basis, pancreatic cancer is somewhat more common in men than women with a corresponding age-adjusted incidence rates to world standard population of 4.6 per 100,000 in men and 3.3 per 100,000 in women (9). It is predominantly a disease of elderly people, and only 12.6% of all patients are diagnosed at age before 55 years old in Surveillance Epidemiology and End Results (SEER) cancer Statistics Review, 2000-2004 (23).

2.2.3 Time trends

The secular trends of pancreatic cancer have varied considerably in the second half of the 20th century worldwide. According to a study of the international variation of pancreatic cancer mortality over the period 1955-1998 (10), in general pancreatic cancer mortality rates among men increased consistently among countries with low pancreatic cancer mortality rates in 1955-1958, including Japan, Southern and Eastern European countries. The rates increased until 1975 or the 1980s, and then decreased or remained stable in countries where the rates were high in the 1950s, such as the Northern European countries, North America and Oceania. Among women, pancreatic cancer mortality has generally increased worldwide during the same period.

In Europe, mortality rates from pancreatic cancer increased throughout the late 1950s and the 1980s with some reversal of trends observed in Britain, Denmark, Sweden, and other Nordic countries in the 1980s (24). Since the 1990s, the increasing trend has apparently declined or levelled off in most European countries (25). The reasons for the declining trends of pancreatic cancer are unclear; it has been postulated to be attributable to the declining trend in smoking rates, especially in men.

Mortality rates for pancreatic cancer are likely to be a good surrogate for incidence rates. However, given the dramatic changes in diagnostic technology and in the clinical management of pancreatic cancer, the reported trends based on mortality should be viewed with caution. One Swedish study observed that, among those notified to the Causes of Death Register but not the Cancer Register, 40% were actually not pancreatic cancer (26). Thus, studies based on mortality (24, 25) may be subject to serious error due to low specificity of the Causes of Death Register (27).

2.3 RISK FACTORS

2.3.1 Tobacco use

2.3.1.1 Cigarette smoking

Cigarette smoking is the most well-established risk factor for pancreatic cancer. In 1985, the International Agency for Research on Cancer (IARC) concluded that cigarette smoking is an important cause of pancreatic cancer (28). Most studies have shown that the risk of pancreatic cancer increases as amount and duration of smoking increase (29-38). The relative risks for pancreatic cancer have ranged between 1.5 and 3 for current smokers versus non-smokers (12, 28, 39-41). It has been estimated that about 25-30% of all pancreatic cancers may be attributed to cigarette smoking (1, 4). In addition, the risk of pancreatic cancer in former smokers is reduced to that of never smokers after about 10-15 years of cessation (38, 42, 43). The rapid reduction in the risk of pancreatic cancer after smoking cessation suggests that tobacco smoke is a late-stage component in the carcinogenic process of pancreatic cancer (12).

Of about 60 identified carcinogens in cigarettes, the nicotine-derived nitrosamine ketone, NNK, is the most potent carcinogen in pancreatic carcinogenesis (44, 45). The mechanisms by which NNK might lead to pancreatic cancer pathogenesis are not completely understood. One of the most well-known features of NNK is the ability of its metabolites to bind to DNA and induce point mutations in the *RAS* gene – mutations that are observed in the majority of pancreatic adenocarcinomas (44, 45).

2.3.1.2 Cigar and pipe smoking

Besides cigarette smoking, little is known about the effects of using other forms of tobacco, including cigar and pipe on the risk of pancreatic cancer. Previous studies have been hampered by the relatively few nonsmokers of cigarettes who used other forms of tobacco. Some studies have reported an increased risk of pancreatic cancer associated with cigar smoking (46-51), but not all (38, 52-54). Likewise, previous results on pipe smoking in relation to pancreatic cancer risk are conflicting. Most studies have failed to find an association between pipe smoking and pancreatic cancer (38, 47, 50, 52-55), with some reporting positive findings (48, 49, 56).

2.3.1.3 Smokeless tobacco

Smokeless tobacco is a form of tobacco that is not burnt when used, and is usually placed in the oral or nasal cavities against the mucosal sites that permit the absorption of nicotine into the human body. There are two main types of smokeless tobacco: chewing tobacco and snuff (moist or dry) (57-59). All forms of tobacco use are addictive. Studies of dependent users show that nicotine exposure is similar in smokeless tobacco users and smokers, often leading to strong physical dependence (60). Despite being classified as carcinogenic, smokeless tobacco is used increasingly in several populations, including Scandinavian countries, particularly in teenagers and young adults (60-63). Among them, Sweden has the highest consumption, predominantly in the form of moist snuff called snus. In 2002, at least 23% of Swedish men used snus (64).

The Swedish snus is claimed to contain less amounts of carcinogenic substances compared to other types of snuff (65). This has fostered a perception that the use of Swedish snus is a harmless alternative to smoking (66, 67). However, epidemiological evidence for this safety is very limited. Smokeless tobacco products are known to cause oral cavity cancer in South Asians (68), although a similar risk has not been shown in Sweden (65). Recently,

accumulating epidemiologic evidence (32, 47, 48, 69) suggests that the use of smokeless tobacco, including Scandinavian snus (69), may increase the risk of pancreatic cancer, although published data are based only on few exposed cases.

With the prospect that snus might become officially approved as a safe substitute for cigarettes (70, 71), valid and precise epidemiologic data on health risks associated with its use are urgently needed. One of methodological issues in studies on snus effects is how to remove the confounding effects caused by smoking, since individuals who combine smoking with using snus may smoke less. To better evaluate the carcinogenic effect of snus alone, analyses need to be done among never-smokers. No previous study had sufficient power to limit the analysis specifically in never-smokers.

2.3.2 Diabetes mellitus

Type II diabetes has been consistently shown to be associated with elevated risks of pancreatic cancer (8, 72), although diabetes can also be a consequence of pancreatic cancer (73, 74). The underlying mechanisms by which type II diabetes increases the risk of pancreatic cancer may be due to elevated postload glucose concentration, hyperinsulinemia and gradual impaired glucose tolerance (8).

At least three prospective studies have directly examined the associations of postload plasma glucose (75), fasting serum glucose (76, 77) and pancreatic cancer risk. All studies have shown approximately a 2-fold elevated risk of pancreatic cancer when the top and bottom categories were compared. All observed a statistically significant dose-response association between glucose levels and pancreatic cancer, which further strongly supports a causal role for type II diabetes in the pancreatic cancer etiology.

2.3.3 Obesity

Recently, obesity is reported to be consistently associated with an increased risk of pancreatic cancer in several large prospective studies (78-80), although not all (81, 82). In 2003, a meta-analysis documented that obesity was a weak but consistent risk factor for pancreatic cancer (83). Another updated systematic review of 21 independent prospective studies on the association between body mass index (BMI) and pancreatic cancer risk also supports a positive association between BMI and the risk of pancreatic cancer in men and women. The estimated summary relative risk of pancreatic cancer per 5 kg/m^2 increase in BMI was 1.12 (95% confidence interval [CI], 1.06-1.17) in men and women combined, 1.16 (95% CI, 1.05-1.28) in men, and 1.10 (95% CI, 1.02-1.19) in women (84). It appears that a high BMI increases the pancreatic cancer risk in men, while there is a weak or no association among women. In fact, among 16 studies (30, 31, 75, 78-81, 85-93) which have reported separated results for women since 2000, only 4 (78-80, 85) have observed a statistically significant increased risk associated with obesity.

One possible reason for the observed gender disparity in the link between obesity and pancreatic cancer may be because women tend to gain weight more peripherally than men. Central adiposity rather than overall obesity measured by BMI may increases the risk of pancreatic cancer. Studies have shown that central adiposity is more strongly correlated with intra-abdominal fat and with increased insulin secretion and insulin resistance (94-96). However, only few studies have investigated the association between central adiposity and the risk of pancreatic cancer (81, 86, 97, 98). Some suggest an increased risk associated with central adiposity measured by waist-to-hip ratio (WHR) or waist circumference (86, 97, 98), but a null result was also noted (81). Therefore, more studies are needed to investigate the relationship between central adiposity and pancreatic cancer risk.

2.3.4 Physical activity

Physical activity has long been known to reduce glucose intolerance, even in the absence of weight loss (99, 100). Thus, it is straightforward to hypothesize that physical activity may decrease the risk of pancreatic cancer. However, a majority of studies failed to detect a statistically significant protective effect of physical activity on the risk of pancreatic cancer. Among at least 14 studies so far (31, 79-82, 88, 89, 91, 92, 97, 101-104) that have reported results on the association between recreational physical activity and pancreatic cancer risk, only 5 studies (79, 88, 89, 102, 103) suggested an inverse association between pancreatic cancer and moderate to vigorous physical activity.

A negative association between physical activity and the risk of pancreatic cancer arose, at least in part, due to misclassification given the complicated nature of the variable physical activity and the changes in physical activity throughout life (99, 105). Optimally, epidemiology studies should identify all body movements and obtain information on dose – intensity, duration, and frequency. However, most studies lack information on all types and specific components of physical activity.

2.3.5 Chronic pancreatitis

An increased risk of pancreatic cancer associated with hereditary pancreatitis has been well recognized (106, 107). It has been reported that the cumulative risk of developing pancreatic cancer by the age of 70 years is around 40% in individuals with hereditary pancreatitis (108). However, the hereditary pancreatitis is a very rare disorder, and only accounts for about 1% of all cases of pancreatitis (109). Most chronic pancreatitis (about 70%) are attributed to alcohol abuse (110).

The findings on the chronic pancreatitis in relation to pancreatic cancer are inconsistent. Two prospective studies (6, 111) have reported that individuals with chronic pancreatitis have an extremely high risk of pancreatic cancer with a standardized incidence ratio (SIR) of more than 16 when compared to general populations, and the SIR remained around 14 even after excluding the first 4 years of follow-up (6, 111). While another study has not provided strong support for a casual role of chronic pancreatitis given their observation of only modest increased risk and the risk was substantially reduced after 10 years of follow-up (112).

The different magnitude of the reported association may be caused by different methodology problems, such as selection bias, ascertainment bias, confounding by smoking or other risk factors (112, 113). However, more new data suggest that chronic pancreatitis, especially hereditary pancreatitits, may be one of the few consistent risk factors for pancreatic cancer (114). It has been proposed that the prolonged inflammation observed in chronic pancreatitis patients may initiate or promote the progression of a pancreatic tumor (110). Due to the relative rarity of this condition in the general population, however, only a small percent (3-4%) of pancreatic cancer may be attributed to chronic pancreatitis (113).

2.3.6 *Helicobacter pylori* infection

Since the first culture of *Helicobacter pylori* (*H. pylori)* by Marchall and Warren in 1982 (115), the bacterium has progressively gained importance and, nowadays, it is recognized as the main pathogenetic factor for chronic gastritis, peptic ulcer disease, gastric carcinoma and MALT (116). It was designated as a class I human carcinogen by the International Agency for Research On Cancer (IARC) in 1994 (117).

Recently, two serology-based case-control studies have shown that *H. pylori* infection is associated with about a doubled risk of pancreatic cancer (118, 119), which suggests a possible relationship between *H. pylori* infection and pancreatic cancer development. Several possible mechanisms by which *H. pylori* infection may increase the risk of pancreatic cancer have been proposed. First, it may be due to changed secretion of certain gut hormones, such as gastrin (increased secretion) or somatostatin (decreased secretion due to low number of antral somatostatin cells resulting from *H. pylori* infection) (118, 119). Both elevated gastrin and diminished somatostatin have been suggested to stimulate pancreatic growth, which in turn, may increase the susceptibility of the pancreas to carcinogens (120, 121). Second, it may be via long-term conditions of excess gastric/duodenal acidity, which involves predominantly gastric antral colonization of *H. pylori*, hyperchlorhydria, uninhibited secretin release, attendant elevations in basal pancreatic bicarconate output and pancreatic ductular hyperplasia with increased synthesis of DNA, possibly linked to a greater susceptibility to carcinogens delivered through the circulation (122). Third, increased formation of N-nitroso compounds by nitrate-reductase-producing bacteria proliferating in the hypoacidic stomach may represent another common pathogenetic mechanism (118, 119, 122). The last possible mechanism for the association between *H. pylori* infection and pancreatic cancer is through chronic inflammation (123), although there is no evidence for direct pancreatic colonization by the organism of *H. pylori.*

For many years, excess acid was believed to be the major cause of ulcer disease. The discovery of *H. pylori* has changed our understanding of the pathophysiology of peptic ulcer disease (124). While acid is still considered significant in ulcer formation, and there is much evidence to support the idea that *H. pylori* infection is a prerequisite for peptic ulcer disease (125, 126). It has been estimated that 95% of the duodenal ulcers and 70% of the gastric ulcers can be attributed to *H. pylori* infection (127). Duodenal ulcer is usually associated with antral colonization of *H. pylori* and hyperacidity, whereas gastric ulcer is linked to infection of the gastric corpus resulting in a tendency towards hypochlorhydria (128). Hence, the two types of peptic ulcer could be used as markers to test two different plausible mechanisms (hyperacidity or intragastric N-nitrosamine formation) for enhancement of pancreatic carcinogenesis by *H. pylori*. However, findings from previous epidemiological studies on the association between peptic ulcer disease and pancreatic cancer risk are inconsistent. Some studies have shown an elevated risk of pancreatic cancer among patients with duodenal ulcer, or with ulcers in general (53, 129-131), while some have failed to confirm this association (132-135).

In addition, patients with a remote partial gastrectomy for peptic ulcer disease may also have an increased risk of pancreatic cancer by an increased production of N-nitroso compounds in the operated stomach (136). However, previous results on partial gastrectomy are also conflicting, with some reporting an increased risk of pancreatic cancer (131, 132, 137-142), but not all (133, 143, 144).

In recent years, there is increasing evidence of an association between infection with other *Helicobacter* species with various extragastric diseases, including biliary tract cancer, chronic liver disease, or hepatocellular carcinoma in humans (145-148). Since the exocrine pancreas interacts closely with the hepato-biliary tract, a new hypothesis emerges that infection of other *Helicobacter* species may be involved in its carcinogenesis process. This hypothesis is supported by a small Swedish study which identified *Helicobacter* genus-specific DNA other than *H. pylori* in five of six pancreatic ductal adenocarcinoma biopsy specimens (149). Another study also detected *Helicobacter* DNA more commonly in pancreatic cancer compared with normal pancreas or pancreas from patients with other diseases (123).

2.3.7 Non-steroidal anti-inflammatory drug

Experimental studies have suggested that aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) may inhibit pancreatic carcinogenesis (150, 151). However, limited findings from observational studies have been inconsistent, ranging from a significantly increased association between regular aspirin use and pancreatic cancer risk (152), to a significant inverse association (153). A recent meta-analysis of 11 studies has shown that neither use of aspirin, non-aspirin NSAIDS, nor overall NSAIDs was associated with the risk of pancreatic cancer (154).

2.3.8 Dietary factors

It has been estimated that 30-50% of pancreatic cancer may be attributed to dietary factors (155). Numerous epidemiologic studies have examined the relationship between dietary patterns, food groups, or individual nutrients and pancreatic cancer; however, findings have been largely inconclusive (12, 39, 40). The most consistently observed finding is the inverse association between fruit and vegetable intake and pancreatic cancer risk (156). However, in a recent report based on combined data from two large cohort studies, consumption of a "prudent" diet (high fruit and vegetable intake) compared to a "Western diet" (high meat and fat intake) has showed no reduction in the risk of pancreatic cancer (157), while another Canadian study found a significant inverse association between the fruits and vegetables dietary pattern and the risk of pancreatic cancer in men (158).

2.3.8.1 Fruits and vegetables

It is possible that certain components of fruits and vegetables, such as vitamin C or folic acid, may be related to the risk of pancreatic cancer. Evidence from *in vitro* and animal studies indicates that impaired methyl group metabolism can influence cellular differentiation in the pancreas, and in turn contribute to toxic damage in ways that promote the pathogenesis of pancreatic diseases and carcinogenesis (159). Therefore, it has been hypothesized that dietary factors involved in methyl group metabolism, such as folate, vitamin B6, B12, and methionine, may modify cancer risk (160). A recent meta-analysis of 5 published studies (1 case-control and 4 cohort studies) found a significant protective benefit from dietary folate for pancreatic cancer. The summary relative risk for the highest versus the lowest category of dietary folate intake was 0.49 (95% CI, 0.35-0.67) (161). A recent study (162) based on four large cohorts in the United States did not support a clear association between the risk of pancreatic cancer and circulating levels of one-carbon nutrients, including plasma folate, vitamin B6, vitamin B12, and homocysteine. However, there was a modest inverse trend between folate, B6, and B12 and pancreatic cancer risk among participants who obtained these nutrients exclusively through dietary sources, particularly among people who maintained a normal BMI. Another recent study (163) also observed that methionine intake was significantly inversely associated with the risk of pancreatic cancer. These findings lend further support to the hypothesis that reduced methyl group availability may play a role in the pancreatic carcinogenesis.

2.3.8.2 Meat and fat intake

Previous findings on the relation between meat or fat intake and pancreatic cancer risk have been inconsistent (40). Some studies suggest that higher cholesterol intake (164), total meat intake (165), or saturated fat (166) are associated with an increased risk, but others report null results (167). It has been suggested that different practices of cooking or processing meat may have an effect on the pancreatic cancer risk (168-170). Cooking meat at high temperature can result in formation of heterocyclic amines (HCA), and meat processing

(curing or smoking) can increase N-nitroso compounds. Two recent studies (171, 172) directly investigated the association between dietary exposure to food mutagens and the risk of pancreatic cancer, and found that HCA and polycyclic aromatic hydrocarbons (PAH) derived from meat cooked at high temperatures were associated with an increased risk of pancreatic cancer, which further supports the hypothesis that dietary mutagen exposure may increase the risk of pancreatic cancer.

2.3.8.3 Carbohydrates and glycemic load

Recent studies on pancreatic cancer suggest that glucose intolerance and insulin resistance may play a role in the carcinogenesis, thus, dietary factors that increase postprandial plasma glucose levels may have a direct impact on pancreatic cancer. A number of studies have examined the relation between carbohydrate intake and the risk of pancreatic cancer, but findings have been inconsistent (40). Recently, at least four prospective cohort studies (173-176) have examined the relationship between glycemic load or index and pancreatic cancer, but none showed an overall association, except for Michaud's study (174) which reported a relative risk of 2.63 (95% CI: 1.02-6.99) comparing the highest to the lowest quartile of glycemic load among women with a BMI greater than 25 and low physical activity.

2.3.8.4 Alcohol

Heavy alcohol consumption is strongly associated with chronic pancreatitis (177, 178), which has been indicated as a risk factor for pancreatic cancer (6, 7). Therefore, alcohol has been suggested to play a role in the carcinogenesis of pancreatic cancer through development of chronic pancreatitis. However, the available evidence for an association between pancreatic cancer and alcohol consumption is not convincing (179, 180). In 2001, a meta-analysis of 17 studies found no association between alcohol intake and pancreatic cancer risk (181), although some studies have reported an increased risk for heavy alcohol drinkers or certain type of alcohol (165, 182). Given that smoking and alcohol are highly correlated, some of the elevated risks in these studies may be due to residual confounding by smoking (40, 183).

2.3.8.5 Coffee and tea

Coffee, as a popular beverage, has been thoroughly investigated for procarcinogenic and anticarcinogenic effects over the last four decades (184, 185). The possible association of coffee consumption and pancreatic cancer risk gained widespread attention following a large study published in the early 1980s which showed a strong positive association (54). However, most subsequent studies could not confirm this finding (184, 185). After reviewing the studies available by 1991, the IARC working group concluded that the literature provided little evidence to support a causal relation between coffee and the risk of pancreatic cancer (184).

Another popular drink - tea, especially green tea, contains polyphenolic compounds which have antioxidant and other beneficial properties. Although protective effects of green tea on pancreatic cancer have been suggested in several *in vitro* studies (186, 187), and animal models (188, 189) , most epidemiological studies have failed to demonstrate any protective effects (182, 190, 191).

2.3.9 Occupational exposures

A wide spectrum of occupational exposures have been related to the risk of pancreatic cancer in epidemiologic studies, however, no single exposure has been confirmed to increase the risk of pancreatic cancer (192). Results from a meta-analysis suggest that the risk of

pancreatic cancer may be increased by occupational exposure to chlorinated hydrocarbon (CHC) solvents, nickel, chromium, PAHs, organochlorine insecticides, and silica dust (193). In another meta-analysis of 14 epidemiologic studies examining pancreatic cancer risk among workers exposed to formaldehyde, there is no increased risk among industrial workers who had the highest formaldehyde exposures, although a slight increase was observed among embalmers, pathologists and anatomists (194). Overall, these findings suggest that certain occupational exposures may be related to pancreatic cancer, but these are unlikely to play an important role in the etiology of pancreatic cancer.

2.4 TUMOR MUTATION AND GENETIC SUSCEPTIBILITY

2.4.1 Tumor mutation

It has been proposed that in order to develop pancreatic carcinoma, the pancreatic carcinogenesis may include multiple mutations in a single cell, including overexpression of receptor-ligand systems, oncogene activation and loss of tumor suppressor genes (195, 196). The main oncogene involved in pancreatic carcinogenesis is K-*ras* mutation with overall frequencies of 50-90% among all pancreatic cancer cases (197, 198). It has been reported in a meta-analysis (198) that the frequency of codon 12 K-*ras* mutations in pancreatic intraepithelial neoplasia (PanIN) lesions corresponds to their grade of dysplasia, with a significantly higher frequency of mutations in PanIN-2 and PanIN-3 lesions than that in PanIN-1A, indicating that the activation of K-*ras* is essential for pancreatic carcinogenesis, and seems to occur at an early step of its carcinogenesis (198, 199). Several molecular pathology studies have suggested that some lifestyle and environmental factors may cause pancreatic cancer through the activation of K-*ras* (200-205).

The most commonly mutated tumor suppressor genes in pancreatic cancer are p16, Smad4 and p53 (206). The inactivation of *p16* is associated with progression to higher grades of dysplasia, which increases the selective advantage of subsequent mutation in Smad4 (195, 206). The tumour suppressor gene *p53* is one of the critical barriers blocking progression of PanIN initiated by K-*ras.* Thus, the inactivation of *p53* is suggested to be a rather late event in pancreatic carcinogenesis (207).

2.4.2 Genetic syndromes

Several genetic syndromes have been linked to pancreatic cancer development, including chronic hereditary pancreatitis, *BRCA2* germline mutations, familial atypical multiple mole melanoma syndrome (FAMMM), hereditary non-polyposis colorectal cancer (HNPCC) and Peutz-Jeghers syndrome. However, less than 10% of pancreatic cancers are thought to be directly hereditary (1, 208).

2.4.3 Genetic polymorphisms

Several polymorphisms, which are involved in carcinogen metabolism, have been studied in relation to pancreatic cancer (209-213), including cytochrome P450 genes *(CYP1A1, CYP1A2, CYP2D6, CYP2E1)*, glutathione *S*-transferase genes *(GSTM1, GSTT1, GSTP1), N*-acetyltransferase genes *(NAT1, NAT2),* and human uridine 5′-diphosphate glucuronosyltransferases genes *(UGT1A7, UGT1A9).* In general, studies did not detect main effects of these genetic polymorphisms, however, among individuals with specific environmental exposure (e.g. smoking), a possible gene-environment interaction was observed. Duell et al (210) found that the combination of heavy smoking and *GSTT1*-null

genotype was significantly associated with an increased risk of pancreatic cancer. Li et al (212) found that heavy smokers with the *CYP1A2*1D* (T-2467delT) delT, *CYP1A2*1F*(A-163C) *C* allele, *NAT1* 'rapid' or *NAT2* 'slow' alleles had elevated risk of pancreatic cancer compared with never smokers carrying the non-at-risk alleles.

In addition to carcinogen metabolizing enzymes, DNA repair genes may also play critical roles in cancer susceptibility. There are at least five DNA repair mechanisms evolved in humans to minimize the consequence of DNA damage, mainly including base excision repair (BER), nucleotide excision repair (NER), homologous recombination (HR), non-homologous end-joining (NHEJR) and mismatch and recombination repair (MMR) (214). A few studies investigated polymorphisms of some X-ray repair cross-complementing *(XRCCs)* genes with pancreatic cancer. *XRCC1* Arg194Trp appears to be involved in early onset pancreatic cancer (214). Another gene of this family, *XRCC2,* is involved in the HR pathway. One study observed a significant effect modification between *XRCC2* polymorphism and smoking status in modifying pancreatic cancer risk (215). Another study (216) examined several selected polymorphisms of DNA repair genes (including *XRCC1*, O^6 –mehylguanine-DNA methyltransferase (*MGMT*), and AP endonuclease 1 (*APE1*)) in relation to the risk of pancreatic cancer, and observed that the *XRCC1*(194) polymorphism had a significant interaction with the *APE1*(Asp148Glu) or *MGMT*(Leu84Phe) polymorphism in modifying the risk of pancreatic cancer, but no main effect was noted. In addition, Xeroderma pigmentosum-D (*XPD*) (Asp312Asn) which is involved in the NER pathway, was also suggested to have a protective effect on smoking-related pancreatic cancer (217).

Polymorphisms in the 5,10-methylenetetrahydrofolate reductase (*MTHFR*) gene are the most extensively studied in the folate metabolic pathway (218), including two common functional polymorphisms of the *MTHFR* gene, C677T and A1298C. A meta-analysis of epidemiologic studies evaluating the association of the two polymorphisms of *MTHFR* with the risk of pancreatic cancer (161), observed that the *MTHFR* 677TT (variant) genotype was associated with an increased risk of pancreatic cancer, but results for *MTHFR* A1298C polymorphism are limited and inconsistent.

3 AIMS

The overall aim of this thesis was to increase our understanding of the etiology of pancreatic cancer with regard to lifestyle factors and infectious agents. Specifically, the following questions were addressed:

- What are the secular trends of pancreatic cancer in Sweden and how does one interpret the trends? (Study I)
- Is Swedish snus associated with an increased risk of pancreatic cancer? (Study II)
- Is obesity, measured by BMI or WHR, associated with an increased risk of pancreatic cancer? (Study III)
- What is the pancreatic cancer risk in patients with gastric or duodenal ulcer? What is the pancreatic cancer risk in patients who have undergone peptic ulcer surgery? Can our data provide any hints on the proposed hypotheses of a link between *H. pylori* infection and the risk of pancreatic cancer? (Study IV)

4 SUBJECTS AND METHODS

4.1 SETTINGS

4.1.1 The Swedish Cancer Register

The Swedish Cancer Register was started by the Swedish National Board of Health and Welfare in 1958, coded according to the 7th edition of International Classification of Diseases (ICD-7). The register also includes information on basis of diagnosis. A code to distinguish accidental findings during autopsy was introduced around 1971-1975. All newly diagnosed malignant tumors must be notified to the register by physicians, pathologists or cytologists. During the first years following the establishment of the register, underreporting decreased and the estimated overall completeness for all malignancies became greater than 98% in 1978 (219, 220), although the completeness of cancer reporting may vary by site. The Swedish Cancer Register does not include death certificate only (DCO) cases (221).

4.1.2 The Swedish Causes of Death Register

The Causes of Death Register holds information on the date of death, as well as the underlying and contributory causes of death of all deceased Swedish residents since 1952. The causes of death are classified according to ICD-7 through 1968, the 8th version of ICD (ICD-8) during 1969-1986, the 9th version (ICD-9) during 1987-1996, and the 10th version (ICD-10) thereafter. The overall completeness of the register is estimated to exceed 99% (222).

4.1.3 The Swedish Inpatient Register

The Swedish Inpatient Register was launched by the Swedish National Board of Health and Welfare in 1964, collecting data on individual hospital discharges. Besides the unique national registration number, each record contains diagnoses at discharge coded according to ICD-7 through 1968, ICD-8 during 1969-1986, ICD-9 during 1987-1996, and ICD-10 thereafter, and surgical procedures are coded according to Swedish Classification of Operations and Major Procedures though 1996 and the Nordic medico – statistical committee (NOMESCO) classification of surgical procedures thereafter. The percentage of the Swedish population covered by the Inpatient Register was 60% in 1969, 85% in 1983, and 100% in 1987 and onwards (223).

4.1.4 The Swedish Population and Migration Register

This register is maintained by Statistics Sweden and contains official Swedish census data since 1960 in computerized form, including current address of all Swedish residents alive at the end of each year. Migrations have been registered since 1968.

4.1.5 The Swedish Construction Workers Cohort

The Construction Industry's Organization for Working Environment, Safety and Health provided outpatient medical services to construction workers all over Sweden between 1969 and 1992. The basic units were stationary or mobile clinics, typically staffed by a few nurses and a physician. The main activity was preventive health check-ups, offered to all blue-collar and white-collar workers in the building industry through regular (every second year during the first years, every third year thereafter) personal invitations or advertisements at virtually all major building sites (224). Approximately 75% of all employees in the industry were registered in the Construction Workers Cohort. Data from these health check-ups is computerized since 1971.

The total number of visits in the register is over 1,150,000 representing 386,000 individuals. The average number of visits was three, and some individuals had up to 12 visits.

4.1.6 The Women's Health Initiative

The Women's Health Initiative (WHI) is an ongoing, ethnically and geographically diverse, multi-center clinical trial and observational study designed to address some of the major causes of morbidity and mortality in postmenopausal women. Briefly, a total of 161,808 women ages 50 to 79 were recruited at 40 clinical centers throughout the United States. Recruitment began on September 1, 1993, and ended on December 31, 1998. The WHI clinical trial includes three overlapping components: the Hormone Trial (27,347 women), Dietary Modification Trial (48,835 women), and Calcium/Vitamin D Supplementation Trial (36,282 women). Participants in the observational study were 93,676 women who were screened for the clinical trials but proved to be ineligible or unwilling to participate or were recruited through a direct invitation for screening into the observational study. Details of the scientific rationale, eligibility requirements and baseline characteristics of the participants in the WHI have been described elsewhere (225-229).

In the Women's Health Initiative cohort, participants in the clinical trial were followed through regularly scheduled examinations to ensure timely ascertainment of updated medical histories. All women participating in the clinical trial were expected to attend annual clinic visits, with intermediate 6-month mail, phone or clinic contacts. The observational study participants were contacted annually by mailed self-administered questionnaires in all years except year 3 when the questionnaires were filled out at the clinic visit, to obtain updates of their medical histories and selected exposure data. The completion rate of the observational study annual questionnaires was 93% - 96%.

Initial reports of cancer were ascertained by self-administered questionnaires, and all self-reports of pancreatic cancer were confirmed by review of medical records, including pathology reports (if a biopsy or resection was done). The pancreatic cancer cases were then coded by an experienced SEER coder in accordance with the SEER coding guidelines, Extent of Disease, 3rd edition, January 1998. Primary site and histology were coded using the ICD-O-2.

4.2 STUDY POPULATIONS

4.2.1 All pancreatic cancer cases in Sweden (Study I)

In Study I, we retrieved all incident cases of pancreatic cancer (ICD-7 code 157) diagnosed between 1960 and 2003 from the Swedish Cancer Register, and all deceased individuals with pancreatic cancer classified as their underlying cause of death during the same period from the Swedish Causes of Death Register (ICD-7, 8, 9 code 157, ICD-10 code C25 but not C254).

In total, during the period 1960-2003, 46,257 incident cases and 53,686 deceased cases of pancreatic cancer were extracted from the Cancer Register and the Causes of Death Register, respectively.

4.2.2 Swedish male construction workers (Study II)

In study II, the study population was based on the Swedish Construction Workers Cohort. In the Construction Workers Cohort, two different questionnaires were used to collect

information on smoking and snus use in the period 1971-1975 and the period 1978-1992, with no information in between. In the questionnaires used during the first period, non-smokers were not required to indicate that they did not smoke; instead, they were instructed to simply skip the smoking questions. Because all cohort members without answers to these questions were coded as non-users, the never-smoker category may have contained some smokers (230). Because of the ambiguities in the coding of smoking status in the questionnaires used during 1971-1975**,** we restricted our study sample to the workers with at least one visit in 1978-1992 (the first visit defined entry to the cohort), when detailed information on smoking and snus use was collected through personal interviews by nurses. We initially considered 300,637 eligible workers. Due to the small number of women (5% of workers), we limited our analyses to men.

Record linkages with nationwide registers of Cancer, Death, Total Population and Emigration enabled us to exclude 334 records with incorrect national register numbers (which could not be found in any of these registers), 2,868 men who had a death or emigration date before entry, and 1,164 men with cancer before entry. We further excluded 1,392 men with incomplete exposure data. The final cohort comprised 279,897 men (Figure 1).

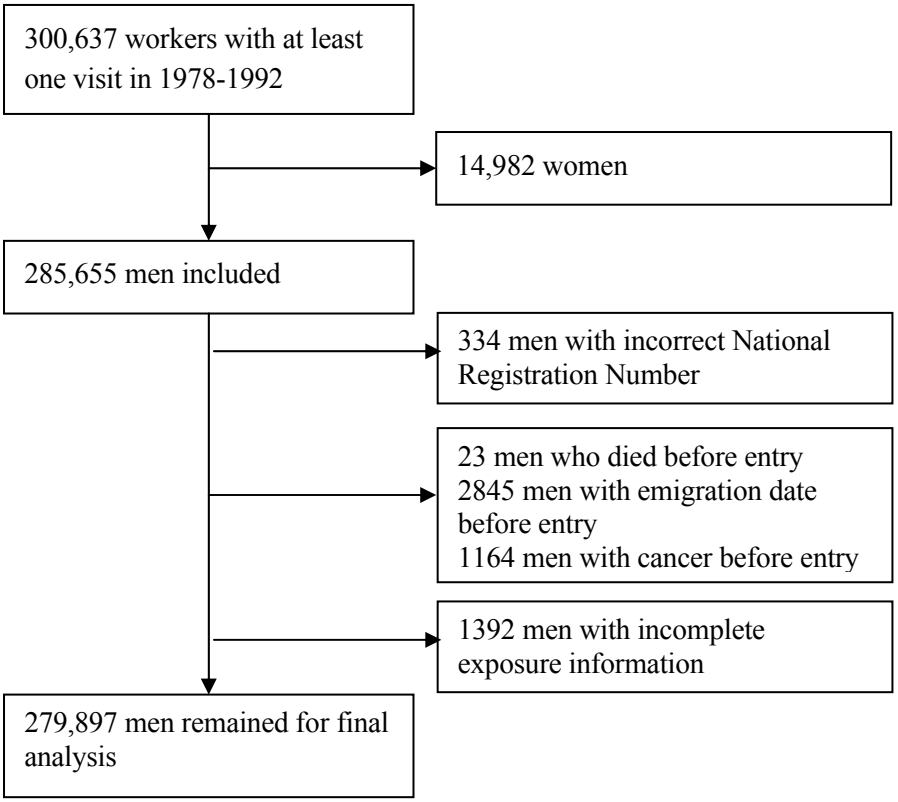

Figure 1. Summary of inclusion and exclusion criteria for Study II - Swedish male construction workers

4.2.3 Postmenopausal women in the United States (Study III)

In Study III, the study population was based on the Women's Health Initiative Cohort. We included all 161,808 participants in both the clinical trial and observational study of the Women's Health Initiative. After excluding 14,849 women who had a history of cancer (except non-melanoma skin cancer) at baseline, 668 women who had no follow-up time, and

7,788 women who had missing values of the main exposures and confounders (including weight, height, waist circumference, hip circumference, smoking, and diabetes) or had implausible values of WHR (WHR<0.4 or WHR>1.2). There were 138,503 women remaining for further analysis.

4.2.4 Hospitalized patients for peptic ulcer disease (Study IV)

This study was based on the Swedish Inpatient Register. We extracted all records of a first hospitalization for peptic ulcer (including gastric ulcer: ICD-7 code 540, ICD-8 and ICD-9 code 531, and ICD-10 code K25, or duodenal ulcer: ICD-7 code 541, ICD-8 and ICD-9 code 532, and ICD-10 code K26) between 1965 and 2003. Through record linkages with other nationwide registers of Cancer, Death, Total Population and Emigration, we excluded patients who could not be found in any of these registers (2.1%), or had prevalent cancers or died during or before the first hospitalization. A total of 181,053 patients remained for further analysis, including 88,338 patients with pure gastric ulcer disease, and 70,516 with pure duodenal ulcer disease. The other 22,199 patients who had more than one type of ulcer were not considered in this study.

All remaining patients were divided into different sub-cohorts, including unoperated pure gastric ulcer sub-cohort, unoperated pure duodenal ulcer sub-cohort, and two operated sub-cohorts, one for gastric resection (operation code 4420-4426, 4429 before 1997; and JDC00, JDC10, JDC11, JDC20, JDC30, JDC40, JDC96, JDC97 from 1997 and thereafter) and another for vagotomized patients (4470-4477 before 1997; and JDG00, JDG01, JDG10, JDG11, JDG96 and JDG97 from 1997 and thereafter). The gastric resection cohort was further divided into Billroth I (4420, 4421, JDC00) and Billroth II (4422, 4423, JDC10, JDC11) group. Patients in the unoperated gastric or duodenal ulcer cohorts who underwent definitive ulcer surgery during follow-up were censored from their respective cohorts and moved to the gastric resection or vagotomy cohort on the day of discharge after surgery. The flow chart for generating different sub-cohorts and the number of patients in each sub-cohort is shown in Figure 2.

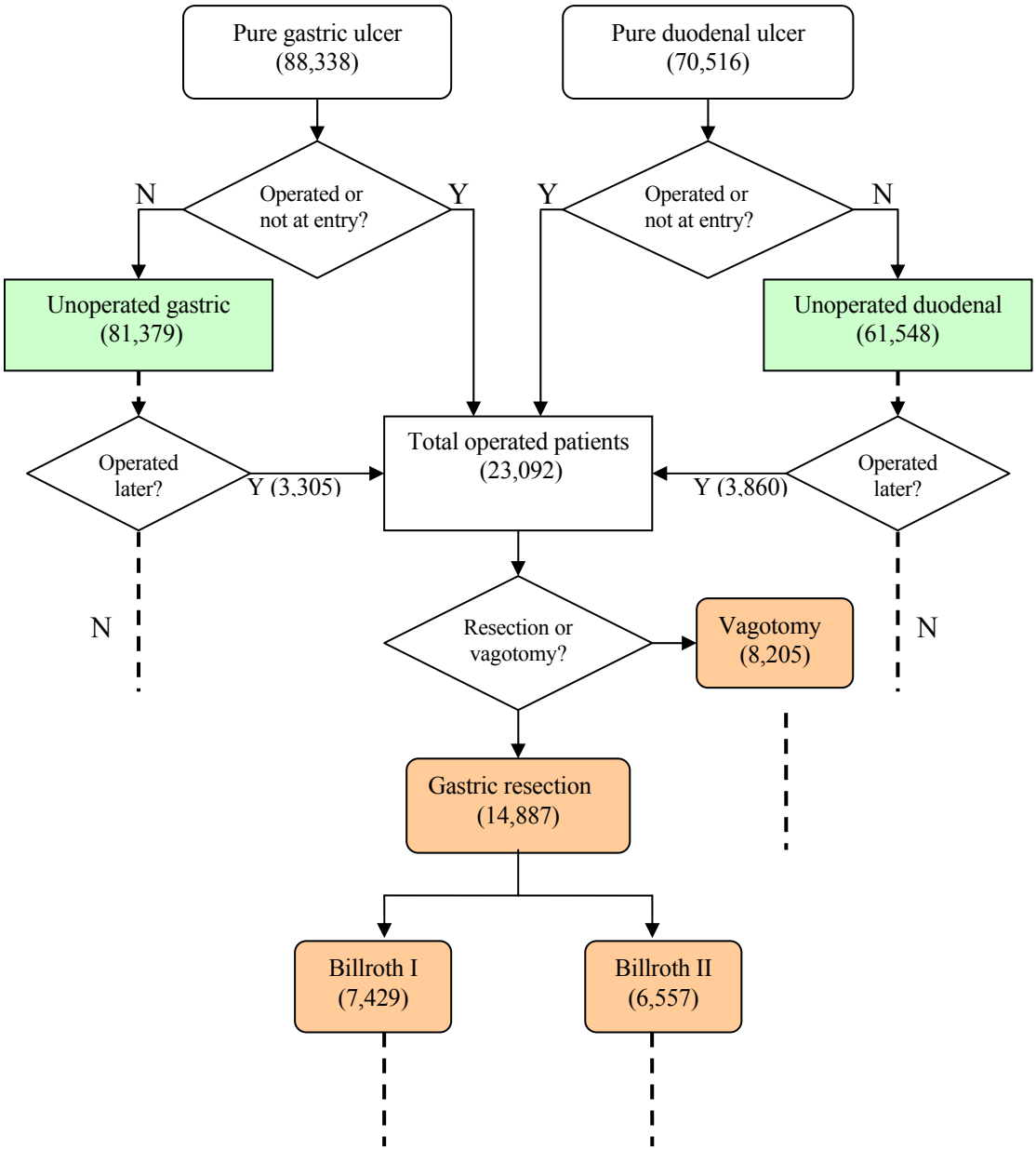

Figure 2. Flow chart for generating different sub-cohorts among all peptic ulcer patients (Study IV)

4.3 MEASUREMENTS

4.3.1 Study II (Construction workers cohort)

All information in the Swedish Construction Workers cohort was collected by questionnaires through personal interviews by nurses. On average, each worker in our study population underwent 2.6 (range 1-9) health check-ups; however, failure to show up in the next check-up may be associated with exposure status and occurrence of outcome. Thus, we only used exposure information obtained at the first visit, which defined entry into the cohort, including snus use status (never, previous, current), and grams of snus per day (<10, ≥10), smoking status (never, previous, current), grams of smoking tobacco per day (continuous) and body mass index (BMI: <25, 25-29, or ≥ 30). Smoking information here combined cigarette, pipe or cigar smoking. If one had smoked any of the three types of tobacco at the time of check-

up, then smoking status was coded as "current"; if one never smoked any of them, then smoking status was coded as "never"; otherwise, smoking status was set as "previous". The amount of smoking tobacco was set to 1 gram for one cigarette, and 6 grams for each cigar. The quality of exposure data has been reviewed previously and was deemed satisfactory (224).

4.3.2 Study III (Women's Health Initiative)

In the Women's Health Initiative, all anthropometric measurements, including height, weight, hip and waist circumferences, were measured by trained and certified staff. Again, we only used exposure information at baseline, because hip and waist circumferences were measured for all participants only at the baseline. The main exposure of interest was obesity. We calculated BMI as an indicator for general obesity, and used WHR or waist circumference alone as measurement of central adiposity.

Other potential confounding variables included age at enrolment (<55, 55-59, 60-64, 65-69, 70-74, 75-), smoking status (never, former smoking (quitted ≥ 30years, quitted 20-<30 years, quitted 10-<20 years, quitted <10 years), current smoking (<5 cigarettes per day, 5-14 cigarettes per day, 15-24 cigarettes per day, 25 and more cigarettes per day), and history of diabetes while not pregnant (yes or no), physical activity (no activity, some activity of limited duration, 2 - <4 episodes per week, 4 or more episodes per week), and information on different treatment assignments (active or placebo) in different clinic trials.

4.3.3 Study IV (Hospitalized peptic ulcer patients)

In the Inpatient Register, except for information on diagnoses at discharge and surgery procedures performed, other information includes patient's age, gender and date of hospitalization and discharge, etc.

4.4 STATISTICAL ANALYSIS

4.4.1 Frequency measurements (Study I)

All incident pancreatic cancer cases from the Cancer Register were used to estimate incidence rates while all deceased cases with pancreatic cancer as underlying cause of death in the Causes of Death Register were used to estimate mortality rates. The denominators for the incidence and mortality rates of pancreatic cancer were based on the Swedish population in 5-year age groups for each calendar year from 1960 to 2003. In order to compare incidence and mortality rates throughout the study period, incidence and mortality rates were standardized over calendar years to the age distribution of the world standard population (231).

For sensitivity analysis, age-adjusted minimum and maximum rates were also estimated. The minimum rates were based on cases found in both the Cancer Register and the Causes of Death Register, and the maximum rates were based on cases found in either register. All analyses were stratified by sex.

4.4.2 Poisson regression model (Study I, Study IV)

The Poisson regression model is a log-linear regression model, in which the number of events is treated as dependent variable, other explanatory variables as independent

variables, with an offset equal to the logarithm of population or person-time. In the Poisson regression model, the number of events in a fixed time interval is assumed to follow a Poisson distribution, provided that the rare events occur at random, independently in time and at a constant rate.

The Poisson regression model was used for age-period-cohort analysis in Study I. Age-period-cohort analysis is one of statistical techniques for understanding temporal trends of an outcome, such as cancer incidence, in terms of three related time variables: age, birth cohort, and calendar period. Early applications of this idea usually presented data graphically, but more recently, investigators have also employed modeling to better understand the separate contributions of each of these factors. However, estimates of each of the three linear effects of age, period, and birth cohort in the presence of the other two are affected by the well-known identifiability problem, due to the exact linear dependence among these three factors (232-234). In our study, we used Poisson regression models for age-period-cohort analyses with the number of events as dependent variable, logarithm of the population as offset, and age (35-39, 40-44, … , 70-74), period (1960-64, 1965-69, … , 2000-03) and corresponding birth cohort (from 1885-1894 to 1965-1973) as independent variables (232-235). Deviances of different models were compared to check the model fit. The Akaike information criterion (AIC) (236, 237) was used to enable the comparison of models of different complexity, with the smaller value indicating a better fit. Because of the identifiability problem of the age-period-cohort model, we estimated curvature effects instead, as these are identifiable parameters representing departure from linearity factors (232).

The Poisson regression model was also employed to estimate relative effects on the standardized incidence ratios (see below) by different explanatory variables in Study IV. To separate effects of explanatory variables, we estimated relative effects on the standardized incidence ratios using a multivariate Poisson regression method with the observed cases as a dependent variable, logarithm of expected cases as offset and other explanatory variables as independent variables, including duration of follow-up, period of index hospitalization, age at entry, gender and complications of ulcer (238).

4.4.3 Cox proportional hazards regression model (Study II, III)

The associations between exposure variables and risk of cancer were expressed as relative risks (RRs) derived from Cox proportional hazards regression models, with attained age as time scale (239). When examining snus use as a risk factor for pancreatic cancer (Study II), in order to better control the strong confounding effect of smoking, we focused on fitting models restricted to never-smokers.

In assessing obesity as a risk factor for pancreatic cancer (Study III), we adjusted for age, different treatment assignments and smoking status. Since diabetes could conceivably be in the causal pathway between obesity and the risk of pancreatic cancer, we performed analyses both adjusted and unadjusted for this factor. We also tested interactions between WHR/waist circumference and smoking status or diabetes history by entering multiplicative interaction terms into the model. In addition, to eliminate the possible influence of undiagnosed cases having experienced weight loss before completing the baseline questionnaires, we also performed sensitivity analyses that excluded the first 2 years of follow-up in the obesity study.

The proportional hazards assumption was tested and satisfied in both Study II and Study III for all exposure variables and potential confounding variables based on graphs of scaled Schoenfeld residuals (240).

4.4.4 Standardized incidence ratio (Study IV)

The standardized incidence ratio (SIR) – the ratio of the observed to the expected number of cancers – was used as a measure of relative risk in Study IV. The expected number of cancers was calculated by multiplying the observed person-time in age- (in 5-year groups), gender- and calendar period-specific strata by the corresponding stratum-specific cancer incidence rates derived from the entire Swedish population. Since the incidence in the observed cohort was compared with the incidence in the corresponding population strata, the SIRs are inherently adjusted for confounding by age at follow-up, gender and calendar period. The 95 percent CIs for SIR were calculated on the assumption that the observed number of events followed a Poisson distribution (238).

Stratified analyses were performed by follow-up duration, sex, presence of complications (bleeding or perforation), calendar period of index hospitalization (before vs. after 1980), age at entry (<50, 50-69, 70-), the calendar period of follow-up (before vs after 1990). Chi-square test for linear trends was used to evaluate dose-response relations with duration of follow-up.

5 RESULTS

5.1 TRENDS OF PANCREATIC CANCER IN SWEDEN (STUDY I)

5.1.1 Comparison of cases in two registers

In total, during the period 1960-2003, 46,257 incident cases and 53,686 deceased cases of pancreatic cancer were extracted from the Cancer Register and the Causes of Death Register, respectively. Of the total 46,257 incident cases, 6,514 cases were not found in the Death Register with pancreatic cancer as underlying cause of death, but 1,470 have been registered as a contributing cause of death; 419 were diagnosed in 2003 and might have died in 2004 or later, which were not covered in this study. On the other hand, we found 13,943 cases in the Death Register that were not recorded in the Cancer Register. Altogether 39,743 subjects were in both registers and 60,200 in either register during 1960 to 2003 (Figure 3).

The distribution of gender and age were similar between cases found in the Cancer Register and those in the Death Register. However, compared with cases recorded in both registers, those found in the Death Register only were more likely to be women and older.

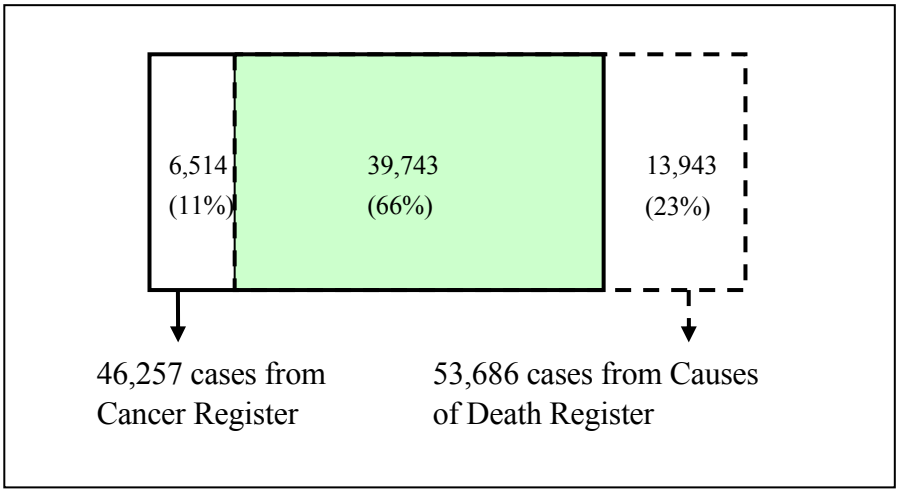

Figure 3. Agreement between 46,257 cases from the Cancer Register and 53,686 cases from the Causes of Death Register; (%) is the percentage among total 60,200 in either register during 1960-2003

5.1.2 Secular trends

Qualitatively, the time trends of age-adjusted rates of pancreatic cancer were similar for incidence, mortality, minimum and maximum rates in both men and women. However, the magnitude of the rates was consistently higher in men than in women. The age-adjusted rates of pancreatic cancer increased in the first study decade (the 1960s) and then peaked for both sexes - with the male peak in the early 1970s and the female peak in 1980s - followed by a steady decline (Figure 4).

In both men and women, the mortality rates were consistently higher than incidence rates during the entire study period, with a more rapid decrease in incidence than in mortality since 1980 (Figure 4). This divergence between incidence and mortality was most pronounced among those aged 75+ years in both sexes (Figure 5).

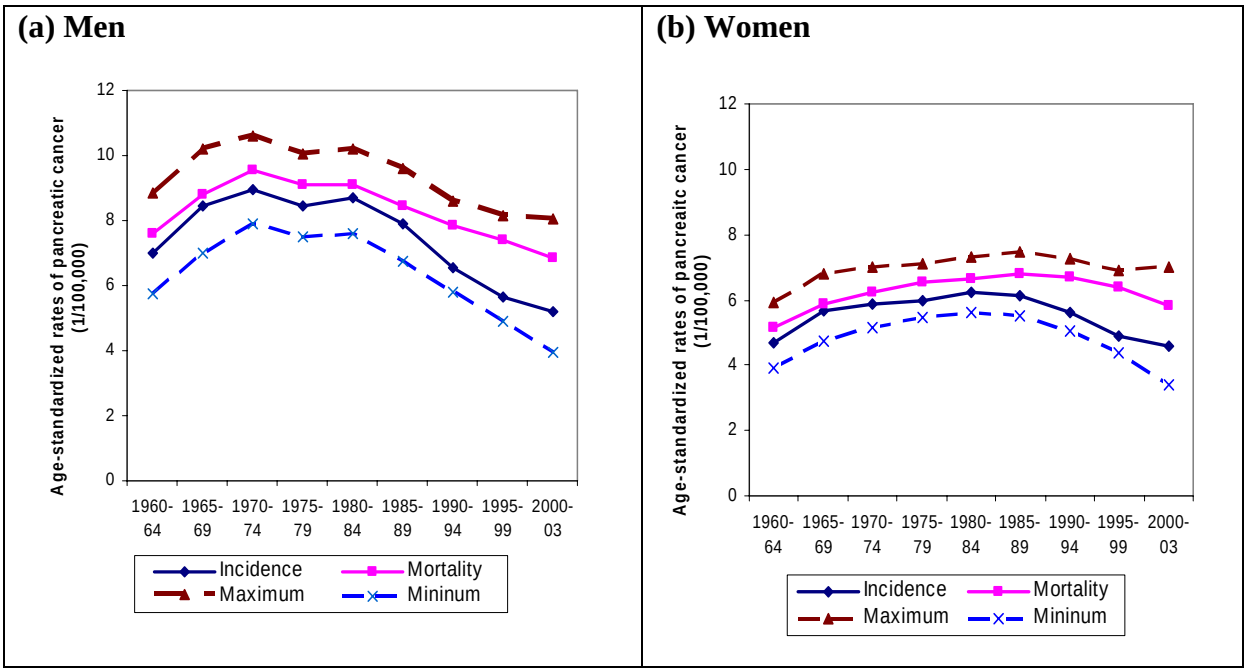

Figure 4. Comparison of age-standardized (to the 1960 world population) incidence, mortality, minimum and maximum rates of pancreatic cancer in 1960-2003 among (a) men and (b) women

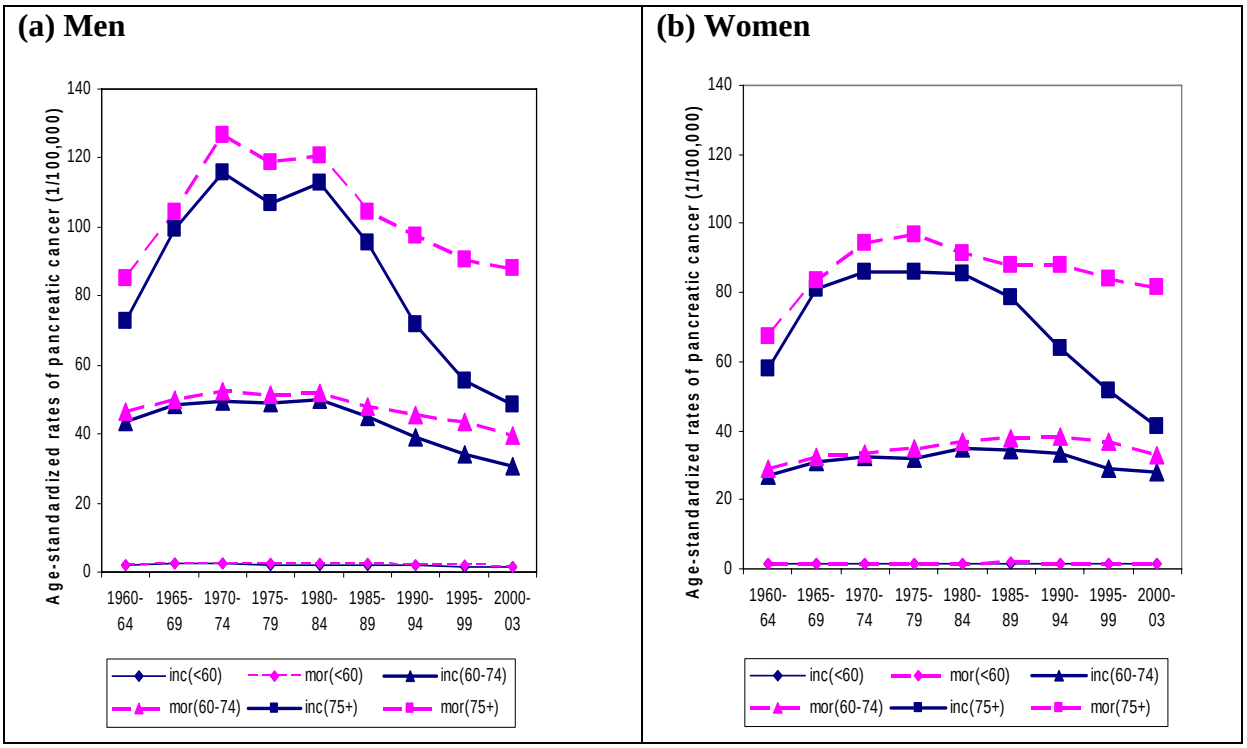

Figure 5. Comparison of age-standardized (to the 1960 world population) incidence rates (solid lines) and mortality rates (dashed lines) of pancreatic cancer by age group among (a) men and (b) women

5.1.3 Age-Period-Cohort model

Poisson regression models were fitted for the 35-74 years age group where the incidence and mortality data was considered more complete and reliable. We observed that an age-period model provided the best fit to the observed trends in incidence and mortality for both males and females according to the lowest value of AIC criterion. This suggests that calendar period explains most of the departure from linearity in trends of pancreatic cancer in Sweden.

Table 1. Comparison of different Poisson regression models for pancreatic cancer incidence and mortality rates among subjects aged 35-74 years in Sweden, 1960-2003

Model		Males				Females			
		Incidence		Mortality		Incidence		Mortality	
(a) Models	DF*	Dev	AIC	Dev	AIC	Dev	AIC	Dev	AIC
Age only	64	411	904	213	712	162	659	147	626
Age-drift †	63	229	724	149	649	161	637	114	595
Age-period	56	64	573	64	578	77	575	52	547
Age-cohort	49	167	690	103	631	125	631	81	590
Age-period-cohort	42	52	589	52	594	51	577	35	558
(b) Test of effects‡	DDF	DDev	*P* value	DDev	*P* value	DDev	*P* value	DDev	*P* value
Drift	1	182	<0.0001	64	<0.0001	0.5	0.5	33	<0.0001
Period curvature	7	115	<0.0001	51	<0.0001	74	<0.0001	46	<0.0001
Cohort curvature	14	12	0.6	12	0.6	26	0.03	17	0.3

* Degrees of freedom

† The combined linear effect of period and birth cohort

‡ Drift effect was estimated by comparing the age-drift model and age model; period curvature effect was estimated by comparing the age-period-cohort model and age-cohort model; birth cohort curvature effect was estimated by comparing the age-period-cohort model and age-period model. DDF and DDev are the difference in degrees of freedom and difference in deviances of the two models compared; *P*-values are based on Chi-square tests.

5.2 SNUS USE AND THE RISK OF PANCREATIC CANCER (STUDY II)

In this study, as of the end of 2004, 468 incident pancreatic cancers were identified over an average of 20 years of follow-up among 279,897 Swedish male construction workers. The average age of the cohort members was 35 years at the time of entry; of those, 31% used or had previously used snus; and the snus use was more common among younger men (<30 years old).

First of all, we confirmed that tobacco smoking was a strong risk factor for pancreatic cancer with a relative risk of 3.5 (95% CI: 2.6-4.6) by comparing current smokers with never users of any tobacco, after adjusting for age (attained age as the time scale), BMI and

snus use (in this analysis, combined use of snus and smoking tobacco was allowed, but exclusive snus use was excluded). When we analyzed data among all cohort members, irrespective of smoking and snus use status, the adjusted relative risk for pancreatic cancer in ever-users of snus was 0.9 (95% CI: 0.7-1.2) compared with never snus users, after adjusting for age (attained age as time scale), BMI, and smoking dose as continuous variable.

In analyses restricted to men who were never-smokers, we found that ever snus use was associated with a doubling risk of the pancreatic cancer (RR=2.0, 95% CI: 1.2-3.3) compared with tobacco abstainers, and there was a significant increased risk with increasing amount of snus use (p=0.01), although the point estimates for the two dose categories above zero did not differ greatly from each other (Table 2).

Table 2. Relative risks (RRs) with 95% confidence intervals (CIs) of pancreatic cancer incidence in relation to snus use, among 125,576 never-smokers

	Pancreatic cancer	
	Cases	**RR* (95% CI)**
Never users of any tobacco	63	Reference
Ever users of snus	20	2.0 (1.2-3.3)
Ex-users	2	1.4 (0.4-5.9)
Current-users	18	2.1 (1.2-3.6)
Amount of snus (grams/day)		
1-9	6	1.9 (0.8-4.3)
10-	13	2.1 (1.1-3.8)
P for trend		0.01

*RR estimates obtained in models adjusted for age (attained age as time scale) and BMI

5.3 OBESITY AND THE RISK OF PANCREATIC CANCER (STUDY III)

As of 12 September, 2005, during an average 7.7 years of follow-up among 138,503 postmenopausal women, 251 incident cases of pancreatic cancer have been identified. At baseline, compared with women with lower WHR, those with higher WHR tended to be older, non-white, and less educated. Women with higher WHR were also more likely to be past or current smokers and tended to smoke more cigarettes per day, to have higher total energy intake, be less physically active, and have higher prevalence of diabetes and hypertension.

Among all tested anthropometric variables, only WHR was significantly associated with the risk of pancreatic cancer whether or not adjusted for diabetes history, although the strength was slightly attenuated in the adjusted model. Based on the model with adjustment for diabetes, the women in the highest quintile of WHR had a 70% excess risk of pancreatic cancer, compared with women in the lowest quintile, and the risk of pancreatic cancer

increased 27% per 0.1 increase of WHR when WHR was analyzed as a continuous variable (Table 3).

In addition, we found that women who were current smokers in the highest tertile of WHR had a 3.7-fold (95% CI: 2.1-6.4) increased risk of pancreatic cancer compared with never smoking women in the lowest tertile of WHR. Further, a significant interaction was detected between smoking status and WHR (p=0.03) (Figure 6). Further stratified analyses by smoking status showed no association between WHR and the risk of pancreatic cancer among never smokers, but significant positive association among ever smokers even when adjusted for the number of cigarettes smoked per day. Finally, we repeated all the above analyses with exclusion of the first 2 years of follow-up; findings remained broadly similar to those from the full analyses.

Table 3. Relative risk (RR) with 95% confidence intervals (CI) of pancreatic cancer by baseline measures of adiposity among 138,799 post-menopausal women

Variable	Cases	Multi-adjusted[1] RR(95% CI)	Multi-adjusted[2] RR(95% CI)
BMI (kg/m^2)			
<22.0	25	0.8 (0.5-1.2)	0.8 (0.5-1.2)
22.0-24.9	62	Reference	Reference
25.0-29.9	84	0.9 (0.6-1.2)	0.9 (0.6-1.2)
30.0-34.9	56	1.1 (0.8-1.6)	1.1 (0.7-1.5)
35.0-	24	0.9 (0.5-1.4)	0.8 (0.5-1.3)
P (trend)		0.5	0.9
Waist (cm) quintile (range, median)			
1 (35.0-74.5, 70.5)	41	Reference	Reference
2 (74.6-81.0, 78.0)	50	1.1 (0.7-1.7)	1.1 (0.7-1.7)
3 (81.1-88.0, 85.0)	46	1.0 (0.7-1.6)	1.0 (0.7-1.6)
4 (88.1-97.4, 92.4)	63	1.4 (1.0-2.1)	1.4 (0.9-2.0)
5 (97.5-194.2, 105.0)	51	1.2 (0.8-1.8)	1.1 (0.7-1.6)
P (trend)		0.2	0.6
Waist (continuous) (per 10cm)	251	1.08 (0.98-1.18)	1.05 (0.95-1.15)
WHR quintile (range, median)			
1 (0.40-0.75, 0.72)	34	Reference	Reference
2 (0.75-0.79, 0.77)	47	1.3 (0.8-1.9)	1.2 (0.8-1.9)
3 (0.79-0.82, 0.80)	44	1.1 (0.7-1.7)	1.1 (0.7-1.7)
4 (0.82-0.87, 0.84)	48	1.2 (0.7-1.8)	1.1 (0.7-1.7)
5 (0.87-1.20, 0.91)	78	1.8 (1.2-2.8)	1.7 (1.1-2.6)
P (trend)		0.002	0.01
WHR (continuous) (per 0.1)	251	1.32 (1.12-1.56)	1.27 (1.07-1.50)

1. Adjusted variables included age, different treatment assignments in clinical trials, and smoking status (never, former smoking (quitted ≥ 30 years, quitted 20-<30 years, quitted 10-<20 years, quitted <10 years), current smoking <4 cigarettes per day, 5-14 cigarettes per day, 15-24 cigarettes per day, 25 and more cigarettes per day).
2. Further adjusted for diabetes history at baseline.

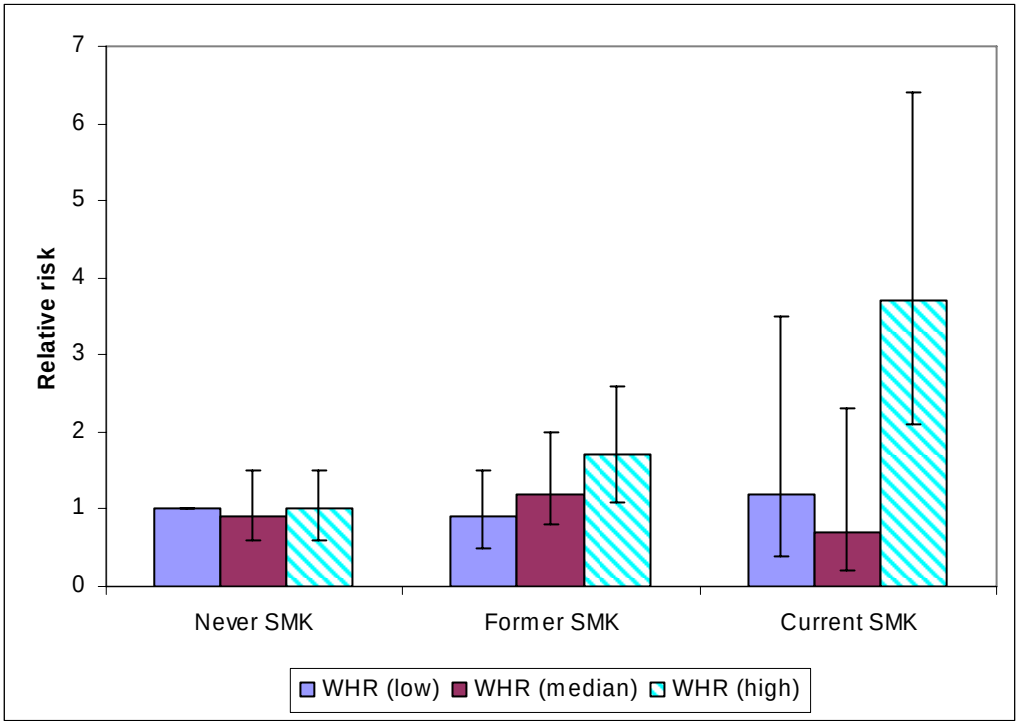

Figure 6. Relative risk of pancreatic cancer in relation to WHR by smoking status (*p* for interaction = 0.03)

5.4 PEPTIC ULCER PATIENTS AND THE RISK OF PANCREATIC CANCER (STUDY IV)

5.4.1 Characteristics of patients in different sub-cohorts

In total, 88,338 patients hospitalized for gastric ulcer and 70,516 patients hospitalized for duodenal ulcer disease were recorded in the Swedish Inpatient Register between 1965 and 2003. Among these patients, 853 incident pancreatic cancer cases were ascertained during follow-up to the end of 2003. As already mentioned in the methods section, all patients were further divided into different sub-cohorts, including unoperated gastric or duodenal patients, and different types of operated sub-cohorts. In addition to patients who underwent surgery during first (index) hospitalization, the operated sub-cohorts also included patients from unoperated patient cohorts who underwent surgery at a later date.

The baseline characteristics of patients and follow-up information in different sub-cohorts are shown in Table 4. Among the two unoperated sub-cohorts, patients hospitalized for gastric ulcer were more likely to be female, older and followed for a shorter period than patients hospitalized for duodenal ulcer. Compared with unoperated patients, operated patients were hospitalized at a younger age, but were followed longer, especially for patients who underwent vagotomy surgery (Table 4).

In this study, smoking prevalence was indirectly assessed in different sub-cohorts by computing the relative risk for lung cancer. The observed elevation of risk for lung cancer indicates that smoking was indeed more common in our cohort than that in the general population, especially among operated sub-cohorts (Table 4).

Table 4. Characteristics of patients hospitalized for peptic ulcer diseases in Sweden, 1965-2003

	Gastric Ulcer	Duodenal ulcer	Gastric resection			Vagotomy
			Total	Billroth I	Billroth II	
No. of patients	81,379	61,548	14,887	7,429	6,557	8,205
Male (%)	42,774 (52.6)	39,721 (64.5)	9,070 (61.1)	3,747 (50.4)	4,832 (74.2)	5,739 (70.0)
Mean age at entry (years)	67	62	56	55	57	48
Mean follow-up (years)	7.2	9.1	15.7	16.5	15.3	17.3
Excluding first 2 years of follow-up						
Person-years	444,971	421,484	203,755	107,848	86,977	124,796
No. of cases	182	135	93	43	46	26
Mean age at diagnosis	73	72	72	71	72	68
SIR for lung cancer (95% CI)	1.8 (1.7-2.0)	1.6 (1.4-1.7)	2.5 (2.3-2.8)	2.9 (2.6-3.3)	2.2 (1.8-2.5)	2.2 (1.9-2.5)

5.4.2 Patients with unoperated gastric and duodenal ulcer

Overall, patients with pure gastric ulcer had a 20% increased risk of pancreatic cancer compared to the Swedish general population. The relative risk rose to 1.5 after 10 years of follow-up. There was a significantly increasing trend with increasing follow-up time (p for trend = 0.03) (Table 5). No significant differences of relative risks were observed by sex, presence of complications, calendar period at index hospitalization or calendar period of follow-up. In addition, in multivariate adjusted Poisson regression, relative risks still tended to increase with increasing follow-up duration, although the trend was not statistically significant (p for trend = 0.1).

We did not observe an increased risk of pancreatic cancer associated with pure duodenal ulcer patients, compared to the general population. Further stratified analyses by sex, presence of complications, calendar period of index hospitalization, age at entry, or calendar period of follow-up did not reveal statistically significant excess risks in any stratum.

Table 5. Standardized incidence ratio (SIR) for pancreatic cancer among patients with gastric or duodenal ulcer

	Pure gastric ulcer			Pure duodenal ulcer		
	No. cases	**SIR**	**95% CI**	**No. cases**	**SIR**	**95% CI**
Overall	182	1.2	1.1-1.4	135	1.1	0.9-1.3
Duration (year)						
2-4	46	0.9	0.7-1.2	39	1.1	0.8-1.5
5-9	66	1.3	1.0-1.7	38	1.0	0.7-1.4
10-14	38	1.5	1.1-2.0	31	1.4	0.9-1.9
15-	32	1.5	1.1-2.1	27	1.1	0.7-1.6
P for trend		0.03			0.7	

5.4.3 Gastric resection and vagotomy

Overall, patients who underwent gastric resection had an 50% excess risk of pancreatic cancer compared to the general population. The risk increased with time since surgery, reaching 2.1-fold 20 years after surgery, but the trend was not significant. Stratified analyses by type of resection revealed a tendency towards higher relative risk among Billroth II patients (Table 6). The relative risks were similar in strata defined by sex or calendar period of surgery in the entire gastric resection cohort, while further substratification by type of resection yielded unstable estimates due to small numbers of observed cancers. Likewise, because of poor statistical precision, multivariate Poisson modelling did not provide additional insight about these relationships.

The relative risk of pancreatic cancer among vagotomized patients was close to unity (95% CI: 0.7-1.5) (Table 6). Stratified analyses by follow-up duration, sex, and calendar period of operation did not reveal excess risks in any stratum.

Table 6. Standardized incidence ratio (SIR) for pancreatic cancer among patients who underwent surgery for peptic ulcer

	Gastric resection						Vagotomy	
	Total		**Billroth I**		**Billroth II**			
	No. cases	SIR (95% CI)	No. cases	SIR (95% CI)	No. cases	SIR (95% CI)	No. cases	SIR (95% CI)
Overall	93	1.5 (1.2-1.9)	43	1.4 (1.0-1.9)	46	1.7 (1.2-2.3)	26	1.0 (0.7-1.5)
Duration (years)								
2-9	41	1.6 (1.1-2.2)	17	1.3 (0.8-2.1)	22	2.0 (1.2-2.9)	12	1.3 (0.6-2.2)
10-19	27	1.2 (0.8-1.7)	12	1.0 (0.5-1.7)	14	1.4 (0.8-2.3)	11	1.0 (0.5-1.8)
20-	25	2.1 (1.4-3.1)	14	2.3 (1.3-3.9)	10	1.8 (0.9-3.3)	3	0.6 (0.1-1.9)
P for trend		0.5		0.2		0.7		0.3

6 DISCUSSION

6.1 METHODOLOGICAL CONSIDERATIONS

6.1.1 Descriptive epidemiology

Epidemiology is defined as the study of the distribution and determinants of disease frequency in human populations (241). The studying of the distribution of disease frequency belongs to the domain of descriptive epidemiology, which involves the analysis of disease patterns according to the characteristics of person, place and time. My first study in this thesis is a descriptive epidemiological study that aimed to examine the secular trends of pancreatic cancer in Sweden.

The main concerns in this study are accuracy and completeness of case ascertainment. Given the major difficulties in diagnosis and dramatic changes in diagnostic technologies for pancreatic cancer, interpretation of either incidence or mortality rate may be hampered by temporal change in accuracy or completeness of case ascertainment. Therefore, we used data from both the Cancer Register and the Causes of Death Register in Sweden to investigate the underlying temporal trends of both incidence and mortality rates of pancreatic cancer which are measured with suboptimal sensitivity and specificity.

First of all, we were puzzled by an unexpected phenomenon that pancreatic cancer mortality rates were consistently higher than incidence rates during the entire study period, and this divergence between incidence and mortality was increasing since 1980 and most pronounced among those aged 75+ years in both sexes. We speculated that this could be explained by several reasons: firstly, low specificity of the Causes Death Register could be one of the main reasons. As reported previously (26, 220), a considerable proportion of the cases notified to the Causes of Death Register actually were not pancreatic cancer, which was mainly caused by inclusion of metastatic disease as a primary tumor in the Register (242). Especially with a continuous decrease in the autopsy rate since 1980 in Sweden (243), classification of cause of death became more liable to error. Many studies have documented significant discordance between medical records, death certificates, and postmortem diagnosis in reporting the cause of death (244, 245).

Secondly, since the Cancer Register does not receive a copy of the death certificate, thus DCO cases are not included in the Cancer Register (221). Although the number of all cancer cases missed in this way amounts to less than 2 percent of all cases in Sweden (219, 220), this practice could cause a large discrepancy between incidence and mortality for a site-specific cancer such as pancreatic cancer. In fact, pancreatic cancer was reported as one of the cancers with higher than average loss to registration (5.6%) in 1978 (220). In addition, due to the changes in health care practices, patients who were old and on clinical grounds considered beyond cure, were increasingly often not examined thoroughly enough to confirm the diagnosis and be reported to the Cancer Register. Hence, the pronounced divergence between incidence and mortality among elderly people could also be attributable to the decreasing completeness of the Cancer Register due to under-notification of older cases.

Taken together, the discrepancy between incidence and mortality of pancreatic cancer in Sweden is more likely due to both the increasing false cases in the Causes of Death Register and the decreasing completeness of the Cancer Register due to under-notification among older cases. It seems that the accuracy is high in the Swedish Cancer Register. In fact, we observed that more than 80% of all pancreatic cancer cases were histologically or

cytologically confirmed in the Register. On the other hand, the Causes of Death Register may be an important source of additional cases to achieve completeness when analyzing the trends in incidence. In addition, since Sweden is the only Nordic country excluding DCO cases from the national Cancer Register, it is crucial to keep in mind the different registration practices when making international comparisons of pancreatic cancer rates.

6.1.2 Analytical epidemiology

The other three studies in the thesis belong to the domain of analytical epidemiology, which involves the analysis of the determinants of disease frequency aiming to identify risk factors for pancreatic cancer. In epidemiology, the strength of the causal relationship between an exposure and a disease is usually measured by relative risk. The overall goal of an epidemiologic study is to get a valid estimation of the relative risk. In order to evaluate whether an estimation is valid or not, three alternative explanations have to be assessed, including bias, confounding, and random error. Both bias and confounding are considered as systematic errors (246). Epidemiological design and analysis strategies are intended to reduce the sources of error, both systematic and random error. The reduction of systematic error improve the validity of the measurement, while reduction of random error could improve the precision of the measurement (247).

6.1.2.1 Study design

Epidemiologic research encompasses several types of study designs, including experimental studies and observational studies. Because experimental studies are usually infeasible, most epidemiologic research is conducted using an observational study design. There are two principal types of observational studies – cohort and case-control studies. The cohort study can be further divided into retrospective (look back in time) and prospective (look forward in time) cohort studies in terms of the timing of events in a study.

Although there is still a debate whether or not register-based study is a retrospective cohort study, here we called it a retrospective study. Three determinant studies in this thesis employed both retrospective and prospective cohort designs. Study II and IV are of a retrospective cohort study design, which took advantage of the Swedish health care system and unique national register number provided to every Swedish resident. The unique national register number enables linking historical records and several nationwide registers together in order to have complete follow-up. Study III is a prospective cohort study with measured exposure variables and detailed information on potential confounders.

Generally speaking, retrospective cohort studies are more efficient (they take less time and money) than prospective studies. However, the major disadvantage of retrospective cohort studies is usually short of information on other key variables, because these studies typically rely on existing records that were not designed for research purposes. In contrast, investigators in a prospective cohort study can usually obtain more detailed information on exposures and other key variables, because they can gather information directly from the participants and have more control of the data collection process. In addition, prospective cohort studies are considered less vulnerable to recall bias because the outcomes have not occurred when the exposures are assessed.

We intended to minimize all possible biases that would distort the estimations of associations; however, due to limitation of the study design, data sources, and other reasons, all three alternative explanations (bias, confounding and random error) are worth discussing.

6.1.2.2 Bias

Although many specific types of bias have been described, there are two broad categories of biases – selection bias and information bias.

6.1.2.2.1 Selection bias

Selection biases can result from procedures used to select subjects or from factors that influence study participation (247). This is a major concern for case-control studies, in which the criteria for selecting controls should be representative of the population that give rise to the cases. However, selection bias can also occur in cohort studies. For example, when loss to follow-up is high and directly related to the exposure and outcome under study; or when the choice of exposed and unexposed individuals is related to developing the outcome of interest.

The loss to follow-up is an ignorable issue in all our studies. In study II and IV, the case ascertainment was done by linking the Swedish nationwide registers, which enabled us almost complete follow-up. In study III, the rate of follow-up was also more than 93%.

However, the possible selection bias raised by the choice of exposed and unexposed individuals related to developing the outcome of interest became one of our concerns. In study IV, such bias would arise if the prevalence of a preclinical pancreatic cancer is higher among patients hospitalized for peptic ulcer disease than those in the general population. Therefore, in this study, in order to minimize the influence of selection bias, the first two years of follow-up were excluded. Similarly, in study III, undiagnosed pancreatic cancer cases might have experienced weight loss before completing the baseline questionnaires; thus, we performed sensitivity analyses after excluding the first 2 years of follow-up.

6.1.2.2.2 Information bias

Information bias can occur whenever there are errors in the measurement of exposure or outcome. The measurement error is usually called classification error or misclassification for discrete variables. It could be either differential or non-differential misclassification, depending on whether the measurement error on one axis (exposure or disease) depends on the other axis (disease or exposure) (247). The bias caused by differential misclassification can either overestimate or underestimate an effect while the bias caused by non-differential misclassification is more likely to dilute an effect.

- Differential misclassification

Our cohort design essentially precludes differential misclassification of exposure among outcome categories. It is also unlikely to assume that misclassification in diagnosis of pancreatic cancer would be related to any of the exposures of interest.

- Non-differential misclassification

However, the non-differential misclassification in our studies is not ignorable. First of all, as mentioned earlier, given the difficulties of diagnosis of pancreatic cancer (248, 249), the possible non-differential misclassification of outcome in all our studies could not be ruled out, which may make our results conservative. However, provided that more than 80% of pancreatic cancers were histologically or cytologically confirmed cases in the Swedish Cancer Register according to the observations in study I, and the case ascertainment in the Women Health Initiative was also centrally adjudicated, we believe that any strong association could not have been missed by the non-differential misclassification of our outcome.

The possible misclassification of exposures in our studies is another concern. In Study II, since we only used information of exposures at baseline, the tobacco use habits may have changed during the follow-up period. Again, this kind of non-differential misclassification is more likely to underestimate an effect. However, our data from the repeat visits suggested that the snus dose remained stable over the follow-up period. A recent Swedish study was also reported a high probability of continuing snus use once the habit has been initiated (250). In addition, a sensitivity analysis suggested that the misclassification of smoking status affected our reported estimates no more than trivially.

In study III, one of the major advantages is that our exposures were actually measured. The measured rather than self-reported exposures are particularly important for waist and hip circumferences, which are likely to be reported less accurately than height and weight. However, since we only used exposure information from baseline measurements, some misclassification of relevant exposures are still unavoidable.

In study IV, we used general population as comparison group. Although the number of exposed people (un-hospitalized patients with peptic ulcer disease) is generally a small proportion of the total population, the admixture of exposed subjects in the reference category which generated our expected incidence rates, again, could lead to substantial underestimation of any true association.

6.1.2.3 Confounding

Confounding is a central concept in observational studies. It is simply defined as the mixing of effects between an exposure, an outcome, and a third variable known as a confounder (246). Since confounding distorts the true association between exposure and disease, it should be controlled either in the design phase, the analysis phase, or a combination of the two (246). In order to control for confounding, except for randomization, we must have information on all potential confounders.

Two studies (Study II, IV) in the thesis are retrospective cohort studies, and as mentioned earlier, the major disadvantage of this type of study is usually lack of information on other key variables. For instance, in Study IV, we lacked information on smoking, and since smoking is associated with both peptic ulcer disease and pancreatic cancer (37, 251, 252), it might have confounded the observed relationship. In this study, we indirectly assessed smoking prevalence in the study population by computing the relative risk for lung cancer. The observed elevation of lung cancer risk indicates that smoking was indeed more common in our cohort than in the general population. However, the relative risk of lung cancer in all sub-cohorts was high in the beginning of the follow-up and remained constant throughout the whole follow-up period, which is different from what we observed for pancreatic cancer – the increasing relative risk with increasing follow-up duration among patients with gastric

ulcer and among patients who underwent gastric resection. In addition, according to Walker AM's study (253), the degree of confounding is very low even though both exposure-covariate odds ratio and confounder-disease relationship are strong (for example, 1.4 apparent relative risk by confounding requires that both the strengths of exposure-confounder and confounder-disease relationship are larger than 3). Thus, the increased risk of pancreatic cancer among gastric ulcer patients may not be completely due to confounding by smoking. Other than smoking, another possible confounding factor in study IV is more extensive use of NSAIDs among peptic ulcer patients. The prevalence of NSAID-associated peptic ulcer disease has increased lately (254). Laboratory studies suggest that aspirin and other NSAIDs may inhibit pancreatic carcinogenesis (151, 255). Accordingly, a negative confounding by NSAIDs leading to underestimation of a true excess risk due to *H. pylori* is conceivable. However, results of epidemiological studies on the relationship between NSAID use and pancreatic cancer risk are inconsistent (152, 153, 256). Use of NSAIDs may be more common among patients with peptic ulcer complications, including bleeding and perforation. However, stratification by presence of complications did not reveal any material difference in the two strata, indicating that confounding by NSAIDs is probably of minor importance.

However, even after controlling for many confounding variables, residual confounding may still be an issue. For example, when the measured confounder is not a perfect measurement, residual confounding will remain. Especially, when the exposure has a weak effect and the confounder has a strong effect, the residual confounding would become an important concern. In study II, because snus use is strongly related to smoking; and in general, people who smoke and also use snus tend to smoke less, when we analyzed a mixed population, it was hard to exclude the negative confounding by smoking dose even when we adjusted for it in the model. Therefore, in order to better control for the strong effect of smoking on pancreatic cancer risk, we focused on never-smokers to estimate independent effect of snus. In addition, we restricted our study population to male construction workers. The restriction allays concerns about confounding by sex, socioeconomic status, and occupational exposures. So far, we were unable to identify any established or suspected risk factor other than smoking that might be linked to snus use, although confounding by dietary factors is possible.

6.1.2.4 Random error

A final concern by which epidemiological studies may draw incorrect conclusions is random error, which is related to precision of the estimation. The primary means of reducing the random error, and in turn improving precision, is to increase the size of the study, although precision can also be improved by modifying the study design to increase the efficiency with a given number of study subjects (247).

Our studies were among the largest studies to date. In study II, the large cohort size and the high exposure prevalence made it possible to obtain meaningful estimates for snus use among never-smokers. In Study III, the large sample size allowed us to examine the interactions between main exposures (central adiposity) and smoking status. The large sample size in Study IV enabled us to detect significant modest effect and examine the pattern of effects over follow-up time. Even though all studies were based on a large size, a chance finding could still not be completely ruled out, especially when we performed stratified analyses in Study III and Study IV, or examined interactions between exposures and other variables in Study III.

6.1.2.5 Interaction

In study III, the interaction between WHR and smoking status was tested by entering an interaction term in Cox regression model, which reflects departure from multiplicativity of the disease risk. Whether or not this is a proper way to evaluate interaction is still under debate.

On one hand, interaction can refer to the biologic interaction of two or more causes of a disease. On the other hand, interaction can refer to statistical interaction (257). It has been argued that the concept of statistical interaction is linked to arbitrariness in the choice of model, because whether statistical interaction is present or not entirely depends on the choice of model or scale. On the other hand, biological interaction is defined to exist if two cause components or two risk factors are involved in the same sufficient causes. It has been shown algebraically that biological interaction results in departure from additivity of the disease rates (247).

In fact, we also tried to test existence of biological interaction (258) between WHR (highest tertile or not) and smoking status (ever smoking or not) on the risk of pancreatic cancer in Study III. The relative excess risk due to interaction (RERI) was 0.97 (95% CI: 0.34-1.60); the attributable proportion (AP) due to interaction was 0.47 (95% CI: 0.21-0.73). Both measurements are not equal to zero, suggesting the existence of a biological interaction. The point estimation of the synergy index (S) was 9.63, far from 1; however, the confidence intervals are wide, due to almost no effect among the highest tertile of WHR alone or ever smoking alone.

6.2 INTERPRETATIONS OF FINDINGS

6.2.1 Interpreting trends of pancreatic cancer

Overall, the time trends in age-standardized rates of pancreatic cancer in Sweden were similar irrespective of whether incidence or mortality rates were used in both sexes. However, the magnitude of the rates was consistently higher in men than in women, as was the speed of the decrease in recent years. The age- standardized rates of pancreatic cancer increased in the 1960s and then peaked for both sexes – with the male peak in the early 1970s and the female peak in 1980s – followed by a steady decline. Our findings are comparable with those reported from England, Wales (259, 260) and North America (10, 261).

In study I, age-period-cohort modeling further supports similar time trends for incidence and mortality rates, and it shows that an age-period model provided the best fit to these rates in both sexes. Period effects potentially reflect changes in diagnostic sensitivity and/or a change in exposure to risk factors that affects all ages equally. As previously reported (24), the increasing rates until the early 1980s may be partly due to improved diagnostic sensitivity and improved notification of the disease, following the introduction of novel non-invasive diagnostic procedures, mainly ultrasound, computerized tomography, ERCP and fine-needle aspiration (14, 15). These changes in diagnosis would most likely create period effects. In addition, we observed similar period curvature effects between men and women, indicating that such changes, as expected, affected males and females equally. However, we observed different trends for age-standardized rates of pancreatic cancer in men and women. This disparity can not be totally explained by the novel diagnostic tools or temporal trends in clinical management, but instead, it is likely to reflect real trends in exposure to risk factors. Although we did not observe a significant curvature effect of birth cohort, there may be a

decreasing or increasing linear trend over the birth cohorts that could not be distinguished from the linear effect of period (232, 233).

Tobacco smoking is the most well-established risk factor for pancreatic cancer, with a 2 to 4-fold increased incidence in smokers as compared with non-smokers (262). Among men, smoking prevalence decreased over the past 30 years, following a peak in the 1960s which preceded the female peak by a decade (263, 264). In parallel with this trend, Swedish men also experienced a notable reduction in smoking-related diseases (265-267). For example, the incidence of lung cancer among men decreased markedly since the mid 1980s, while the rate increased among women with no sign yet of a decrease (263, 266, 268). It is likely that the changes in smoking prevalence also explain, at least partly, the pattern of the trends for pancreatic cancer, especially in males. However, several circumstances suggest that smoking may not be the predominant cause of the temporal changes we observed in pancreatic cancer rates. Firstly, the association between smoking and the pancreatic cancer risk is relatively modest. Secondly, changes in smoking prevalence are more likely to cause birth cohort than period effects. Finally, the temporal pattern of change in pancreatic cancer rates differs from that of lung cancer among women. Hence, other factors may have played a role in these trends.

Recently, infection with *H. pylori* or other *Helicobacter* species was hypothesized to be involved in the carcinogenesis process for pancreatic cancer (118, 119). Maybe the decreasing *H. pylori* infection over time may also account for some of the decreasing secular trends. In addition, while cigarette consumption has reduced significantly in Sweden, the snus consumption has risen significantly at the same time (63). If the suggested link between snus use and pancreatic cancer risk is real, then the increasing snus consumption may also somehow have counteracted the decreasing trends, although the effect of snus may be weaker than that noted for smoking on the pancreatic cancer risk.

In addition, recent studies have shown that obesity is a weak but consistent risk factor for pancreatic cancer (83, 84). The prevalence of obesity has increased in Sweden over the past two decades (269), which may have also counteracted the decreasing trend in pancreatic cancer in recent years. However, given the long latency period of pancreatic cancer, the relatively recent increase in the prevalence of obesity is more likely to be important for future trends.

6.2.2 Snus use and pancreatic cancer risk

The main finding in study II was that never-smoking snus users had a double risk of pancreatic cancer compared with never-users of any tobacco, with some evidence for dose-risk association. The increased risk associated with snus use is in line with a finding reported in a cohort study from Norway (69) – the only published Scandinavian study on the use of smokeless tobacco with pancreatic cancer. In the Norwegian study, a statistically significant 70% excess risk was noted among ever-users relative to never-users of smokeless tobacco, after adjustment for smoking and alcohol use (69, 270).

However, the Norwegian study also noted a 20% reduction in the risk of lung cancer in multivariate-adjusted analysis, suggesting possible residual negative confounding by smoking. In fact, we also observed a significant inverse association between ever snus use and lung cancer (RR=0.7, 95% CI: 0.6-0.7), when we analyzed all cohort members,

irrespective of smoking and snus use status, even after we adjusted for smoking in the model. However, when we restricted the analysis to never-smokers, the association between snus use and lung cancer was absent. The shift from a similar inverse association with lung cancer in the multivariate-adjusted analysis to a null result in the analysis restricted to never-smokers is in good agreement with the Norwegian data and provided further support for the concern on residual confounding by smoking.

The most important strength of our study is that the large cohort size and the high prevalence of exposure to snus made it possible to obtain meaningful estimates in never-smokers, which minimized the confounding effects caused by smoking. The absence of an association with lung cancer in the never smokers stratum, in effect confirms the absence of important confounding by smoking. Thus, we believe that our estimate for snus effect in never-smokers is likely to reflect a valid biological relation, although confounding by other unknown risk factors may not be completely ruled out.

In addition, the smokeless tobacco causing cancer is not biologically implausible. About 30 carcinogens have been identified in smokeless tobacco, and the tobacco-specific nitrosamines (TSNA), formed from nicotine and related tobacco alkaloids, are thought to be particularly important (271). NNK and NNN, the quantitatively dominating TSNAs in snus, have been implicated in the etiology of tobacco-related cancers (44, 272, 273). In addition, a very recent study by Hecht et al demonstrated that a similar exposure to a tobacco-specific carcinogen in smokeless tobacco users and cigarette smokers (274).

There are several reasons for the apparent specificity for pancreatic cancer as the target organ. First, the carcinogenicity of TSNAs is remarkably organ-specific in animal experiments (44). Although the lung and upper respiratory tract dominate as target organs, rats develop pancreatic adenocarcinoma upon exposure to NNK or its metabolite NNAL via drinking water (275). Second, measurable amounts of NNK and NNAL have been documented in human pancreatic juice with significantly higher levels in smokers than in non-smokers (276). Third, it is well established that NNK metabolites bind to DNA and induce activating point mutations in the *RAS* gene – mutations that are observed in 50-90% of all pancreatic adenocarcinomas (45). Fourth, NNK acts as an agonist on β-adrenergic receptors, which activate signal transduction pathways that induce the formation of arachidonic acid and its mitogenic metabolites (45). Fifth, Swedish data suggest a causal link between snus use and risk of type 2 diabetes (277), and there is increasing evidence implicating insulin resistance and abnormal glucose metabolism as risk factors for pancreatic cancer development (75).

Therefore, the Swedish snus investigated in this cohort might not be an entirely safe product, despite its low concentrations of tobacco-specific nitrosamines in comparison with many other smokeless tobacco products. However, because of the special characteristics of our cohort, additional studies in populations with other patterns of use, not the least in women, are desirable in order to put the implications for public health in perspective.

6.2.3 Obesity and pancreatic cancer

In study III, we observed that central obesity measured by high WHR, rather than general obesity measured by BMI, was associated with an increased risk of developing pancreatic cancer among post-menopausal women. Our result was consistent with most previous findings on the association between central obesity and pancreatic cancer (80, 86, 97, 98), although not all (81).

Experimental and observational studies have suggested that insulin resistance and impaired glucose tolerance may play a role in the pancreatic cancer development (73, 75-77, 278-283). An epidemiological study (77) directly examined the relation between prediagnostic serum insulin levels and pancreatic cancer risk and observed a 2-fold increase in risk (RR=2.01; 95% CI: 1.03-3.93) for the highest vs lowest quartile of insulin level after excluding cases in the first 5 years of follow-up. In addition, at least three prospective studies directly investigated the associations of postload plasma glucose (75), and fasting serum glucose (76, 77) with the pancreatic cancer risk; all studies show approximately a 2-fold elevated risk of pancreatic cancer when the top and bottom categories were compared, and all have observed a statistically significant dose-response association between glucose levels and pancreatic cancer risk.

Therefore, one mechanism behind the link between obesity and pancreatic cancer risk might be through insulin resistance, because obesity, especially central obesity, has been linked to significant metabolic abnormalities including insulin resistance, glucose intolerance and diabetes mellitus (99, 284). The insulin resistance induced by excess adiposity cells could lead to reduced levels of insulin-like growth factor binding protein 1 (IGFBP1), probably also IGFBP2, which results in increased levels of bioavailability of insulin-like growth factor 1 (IGF-1). It is hypothesized that the increased insulin and increased levels of bioavailability of IGF-1 may promote cellular proliferation and inhibit apopotosis in many tissue types through insulin receptors and IGF-1 receptor, and in turn, may contribute to tumorigenesis (285).

If this is the mechanism between obesity and pancreatic cancer, then it is not surprising that we observed that high central adiposity rather than high BMI was associated with an excess risk of pancreatic cancer among elderly women. Because, among elderly women, in general, the body fat distribution changes significantly at the time of menopause, with a shift from preferential storage in gluteal/femoral regions to abdominal depots. Our finding further supports that central adiposity may be a better predictor of disease risk than BMI in postmenopausal women (96).

In addition, in this study, we also observed that the WHR-pancreatic cancer association was significantly modified by smoking status – a positive association was only restricted to ever smokers. However, in our data, women who had higher WHR were more likely to be ever smokers and smoked more cigarettes per day. It is possible that the increased risk of pancreatic cancer only among ever smokers with high WHR might be due to, at least partly, residual confounding by smoking dose. To our knowledge, our study is the first to observe the significant interaction between smoking status and WHR. The underlying mechanism behind the synergism effect between smoking and WHR is unclear, although it has been reported that smokers have lower mean BMI compared with non-smokers but have an abnormal body fat distribution with more central adiposity (286-291). More studies are needed to confirm whether the relationship is due to either residual confounding from smoking, or if there is a true interaction between central adiposity and smoking on the development of pancreatic cancer.

6.2.4 Peptic ulcer patients and pancreatic cancer

In study IV, a population-based cohort study, compared with the general population, we observed that unoperated gastric ulcer, but not unoperated duodenal ulcer, was associated with a modest excess risk of pancreatic cancer; and patients subjected to resectional surgery had an elevated risk of pancreatic cancer, and the risk increased with time after operation.

The prior hypothesis for this study was to use the two types of peptic ulcer to test two proposed models behind the link between *H. pylori* infection and pancreatic cancer. One model is proposed to via antral colonization of *H. pylori*, and then hyperchlohydria and pancreatic ducutalar hyperplasia; an other is hypothesized to via colonization of the gastric corpus, leading to hypochlorhydria and increased intragastric N-nitrosamine formation. Thus, we speculated that if the hyperacidity would be the dominating mechanism between *H. pylori* infection and pancreatic cancer risk, then duodenal ulcer disease would be particularly associated with the pancreatic cancer risk. Conversely, if the increased intragastric N-nitrosamine formation would be most important, then gastric ulcer would be most strongly linked to pancreatic cancer development. In addition, we also expected that patients who had undergone peptic ulcer surgery, particularly partial gastric resection, would have an elevated risk since N-nitrosamine formation is increasing in the postoperative stomach (136). Our findings thus lend indirect support to the increased intragastric N-nitrosamine hypothesis, but not to the hypothesis that hyperacidity per se predisposes for pancreatic cancer.

The 50 percent risk increase among patients treated with partial gastric resection is in line with most previous epidemiological studies (131, 132, 137, 141, 142). A conceivable alternative mechanism, instead of the action of endogenously formed N-nitrosamines in the gastric remnant, is recurrent acute pancreatitis due to "afferent loop syndrome" following Billroth II resection (292-295). As suggested in several case reports, occlusion of the afferent jejunal loop results in increased intraluminal pressure that may be transmitted into the pancreatic duct, causing recurrent pancreatitis – a proposed risk factor for pancreatic cancer (6, 111, 296, 297). However, long-term risk seemed to be present also in the Billroth I group, although following the latter procedure there is no afferent loop that can be obstructed.

Despite several strengths in our study, including prospective design, a near complete follow-up and a much larger sample size than in any other previous study, one of major limitations in this study is that we lacked information on other risk factors for pancreatic cancer. Other than the possible confounding by smoking and by NSAIDs as discussed above, lacking information on *H. pylori* infection is another major limitation. Whilst the prevalence of *H. pylori* infection is approximately 95% among duodenal ulcer patients and 70% among those with gastric ulcer, the corresponding prevalence in the general Swedish population ranges from 40% to 60% (298). The admixture of *H. pylori* exposed subjects in the reference category which generated our expected incidence rates could lead to substantial underestimation of any true association.

However, despite suggestive evidence of an association between *H. pylori* infection and pancreatic cancer (118, 119), and despite such an association being biological plausible (118, 119, 122, 123), the causal relationship between this organism and pancreatic carcinogenesis still remains speculative. Previous studies have suggested that other zoonotic *Helicobacter* species may be implicated in the etiology of human hepato-biliary-pancreatic diseases (147, 299, 300), including pancreatic cancer (149). Since these *Helicobacter* species have not been linked to peptic ulcer, they cannot explain the association of pancreatic cancer with gastric ulcer and gastric resection. However, if *H. pylori* is paving the way for – or is just a marker of – some other microbial agent that is involved in pancreatic carcinogenesis, this could give rise to associations of pancreatic cancer with both *H. pylori* and gastric ulcer.

7 CONCLUSIONS

- Changes in health care practices may partly explain the observed secular trends of incidence and mortality rates of pancreatic cancer in Sweden. However, our observation of the gender disparity and the close agreement between incidence and mortality below age 75 strongly suggest a true decline in pancreatic cancer incidence in recent years. This decline is weaker and more recent in women than in men, suggesting gender-specific trends in exposure to environmental risk factors.
- Snus use is associated with a doubled risk of pancreatic cancer. The Swedish snus, despite its comparably low levels of tobacco-specific nitrosamines, may not be an entirely safe product.
- Central, but not general obesity, increases risk of developing pancreatic cancer among postmenopausal women. This result indirectly supports the insulin resistance hypothesis, and suggests that WHR may be a better predictor for the pancreatic cancer risk in postmenopausal women.
- A modestly increased risk for pancreatic cancer was noted among gastric ulcer patients, or patients with gastric resection, especially after prolonged follow-up. This result lends indirect support to the nitrosamine hypothesis, but not to the hyperacidity hypothesis in the etiology of pancreatic cancer.

8 FUTURE STUDIES

Despite considerable efforts in pancreatic cancer research during the past several decades, this malignancy remains a major unsolved health problem. This thesis work adds some understanding of the etiology of pancreatic cancer with regard to lifestyle factors and infectious agents; meanwhile, it raises several questions for further investigating.

In Study II, although our study provides relatively solid evidence that snus is associated with a small but statistically significant excess risk for pancreatic cancer, perhaps the quantification of the strength deserves larger studies to confirm our finding. In addition, because of the special characteristics of our cohort, additional studies in populations with other patterns of use, not the least in women, are desirable in order to put the implications for public health in perspective. In addition, significant higher levels of NNK and NNAL have been documented in pancreatic juice in smokers than in non-smokers, future studies are needed to test TSNAs in pancreatic juice among pure snus users, in order to provide direct evidence for the observed snus-pancreatic cancer association.

In Study III, to our knowledge, this study first detected a synergistic effect between central adiposity and smoking in the etiology of pancreatic cancer. Future studies are needed to confirm whether the relationship is due to either residual confounding from smoking, or if there is a true interaction between central adiposity and smoking on the development of pancreatic cancer.

Moreover, our peptic ulcer study (Study IV) was based on a hypothesis that *H. pylori* infection may increase the risk of pancreatic cancer. However, the causal relationship between this organism and pancreatic carcinogenesis still remains speculative; more studies are needed to directly investigate the association between *H. pylori* or other species of *helicobacter* bacteria and pancreatic cancer, and more desirably, address the possible mechanisms behind them.

Finally, since the etiology of pancreatic cancer is still largely unknown, given that a whole genome scan of common genetic variants for pancreatic cancer called PanScan is under way, it has been expected that the PanScan project will provide excellent information on promising markers for genetic variants related to the pancreatic cancer risk and could lead to considerable further studies of gene-gene, gene-environment, and gene-lifestyle interaction.

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