Gastric Mucosal Abnormality and Risk of Pancreatic Cancer: A Population-Based Gastric Biopsy Cohort Study in Sweden

Jingru Yu[1], Huan Song[2,3], Isabella Ekheden[1], Matthias Löhr[4,5], Alexander Ploner[1], and Weimin Ye[1,6]

ABSTRACT

Background: It remains open whether gastric precancerous lesions are associated with an elevated risk of pancreatic cancer. Our aim was to investigate the association between gastric mucosal status and pancreatic cancer risk.

Methods: Patients with gastric biopsies [normal, minor changes, superficial gastritis, and atrophic gastritis/intestinal metaplasia/dysplasia (AG/IM/Dys)] from the Swedish histopathology registers during 1979 to 2011 were included. Cross-linkages with several nationwide registries allowed complete follow-up and identification of pancreatic cancer cases until 2014. Standardized incidence ratios (SIR) and HRs were estimated.

Results: During 3,438,248 person-years of follow-up with 318,653 participants, 3,540 cases of pancreatic cancer were identified. The same pattern of excess risk of pancreatic cancer compared with the general population was observed across all groups: a peak of 12- to 21-fold excess risk in the first year after biopsy [e.g., normal: SIR = 17.4; 95% confidence interval (CI), 15.7–19.3; AG/IM/Dys: SIR = 11.5; 95% CI, 9.9–13.4], which dropped dramatically during the second and third years, followed by 20% to 30% increased risk after the third year (e.g., normal: SIR = 1.2; 95% CI, 1.1–1.4; AG/IM/Dys: SIR = 1.3; 95% CI, 1.1–1.5). However, no significant excess risk was observed with the normal gastric mucosa as reference.

Conclusions: This unique, large pathologic cohort study did not find evidence that abnormal gastric mucosal status is causally associated with a long-term pancreatic cancer risk. However, a highly increased short-term risk was observed for people undergoing gastroscopy with biopsy sampling compared with the general population.

Impact: Further studies for a long-term risk of pancreatic cancer in patients with gastric biopsies are needed, with further adjustments.

Introduction

Pancreatic cancer is one of the most life-threatening malignancies, with a 5-year survival rate below 9% (1). Reasons of the dismal prognosis are multifactorial, including being asymptomatic until a late stage of carcinogenesis and an aggressive tumor evolution (2). Because of the low resectability rate of pancreatic cancer, detection in the early or premalignant stage is critical. There are some established risk factors, including older age, male sex, chronic pancreatitis, family history, diabetes, smoking, and obesity (3, 4). However, the etiology of pancreatic cancer remains poorly understood. Recently, *Helicobacter pylori* (*H. pylori*) has been considered as another potential risk factor for pancreatic cancer, but the epidemiologic evidence is still inconclusive (5–8), and whether gastric mucosal lesions are also predictive for pancreatic cancer remains open.

Gastric colonization of *H. pylori*, which exists in approximately 50% of the world's population (9), has been accepted as a trigger of successive progression of gastric mucosa, called Correa's cascade, presenting as pathological changes from normal to superficial gastritis, multifocal atrophic gastritis, intestinal metaplasia, dysplasia, and eventually gastric cancer (10). *H. pylori* infection gives rise to superficial gastritis and/or atrophic gastritis due to interaction between host and environmental factors (11). Atrophic gastritis is a chronic condition characterized by long-term gastric inflammation, and atrophy is recognized as a critical step for further progression along the metaplasia–dysplasia–cancer pathway. Our previous nested case-control study found that chronic corpus atrophic gastritis (corpus-predominant) was associated with an increased risk of pancreatic cancer [OR = 1.35; 95% confidence interval (CI), 0.77–2.37] without statistical significance, and the excess risk was particularly marked among participants with both seronegative *H. pylori* and Cytotoxin-associated gene A (CagA; OR = 5.66; 95% CI, 1.59–20.19; ref. 12). A recent Japanese study showed a 3.6-fold increased risk of pancreatic cancer for atrophic gastritis status among smokers with statistical significance, but a nonstatistically significant decreased risk among nonsmokers (6).

Most previous studies have relied on indirect indicators of the progressing derangement of gastric mucosa (*H. pylori* serology, CagA, pepsinogen I/II, etc.). In this study, we aimed to explore the association between gastric mucosal status and pancreatic cancer risk in a large cohort study, which is based on graded morphological assessment of Correa's cascade.

[1]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. [2]West China Biomedical Big Data Center, West China Hospital, Sichuan University, Chengdu, China. [3]Center of Public Health Sciences, Faculty of Medicine, University of Iceland, Reykjavík, Iceland. [4]Department of Clinical Science, Intervention and Technology (CLINTEC), Karolinska Institutet, Stockholm, Sweden. [5]Upper Gastrointestinal Unit, Cancer Division, Karolinska University Hospital, Stockholm, Sweden. [6]Department of Epidemiology and Health Statistics & Key Laboratory of Ministry of Education for Gastrointestinal Cancer, Fujian Medical University, Fuzhou, China.

Corresponding Authors: Jingru Yu, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Nobels väg 12A, Stockholm, Stockholm 17177, Sweden. E-mail: jingru.yu@ki.se; and Weimin Ye, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Nobels väg 12A, Stockholm, Stockholm 17177, Sweden. E-mail: weimin.ye@ki.se

Materials and Methods

Study design

This is a population-based retrospective cohort study. Proceeding from computerized registration at all pathology departments in Sweden, we identified all records of gastric biopsies taken during routine gastroscopy between January 1, 1979, and December 31, 2011 (13). Each entry in the histopathology registers contains biopsy date, biopsy department, age, sex, and the patient's unique personal identity number (PIN; ref. 14). Moreover, each entry also contained all pathological–anatomical diagnoses made by pathologists, using the Systematized Nomenclature of Medicine (SNOMED) morphology and topography codes, as described previously (13). We used the PINs to link this biopsy cohort to the Swedish cancer (15), cause of death (16), and total population registers (17). If the PINs in the biopsy cohort did not match with the Total Population Register, the records were excluded. Also excluded were records with invalid SNOMED codes, birth after or death before first biopsy, sex inconsistence in the different registers, as well as age below 18 or above 90 years (due to few pancreatic cancer cases in this age group). All study patients were followed from date of first biopsy after 1979 until either pancreatic cancer or censoring due to gastric cancer, gastrectomy, emigration, any other cause of death, or end of follow-up (December 31, 2014), whichever came first. This workflow is summarized in **Fig. 1**.

Ascertainment of exposures

On the basis of the graded morphologic assessment of Correa's cascade of patients' gastric mucosa at first registration, we grouped participants based on their SNOMED morphology codes into normal (M001**), minor changes (other M0 or M1/M2/M3****, but not M38***), superficial gastritis (M38***, M4****), atrophic gastritis (M58***), intestinal metaplasia (M73320), and dysplasia (M74***). The latter three categories were combined into one group (AG/IM/Dys) to preserve statistical power. This categorization constituted the exposure of interest. When multiple diagnoses of one biopsy were present, we grouped patients according to the most advanced lesion. Patients with a history of gastric cancer or gastrectomy at baseline were excluded, because the surgical treatment typically involves major rearrangements of the anatomy and physiology of the proximal gastrointestinal tract, and follow-up entails a high probability of both surveillance bias and outcome misclassification. Information on gastric cancer and gastrectomy was ascertained from the Cancer Register [International Classification of Diseases (ICD) version 7, 151] and National Patient Register (operation codes before 1997: 4411–4419, 4420–4426, 4429; operation codes since 1997: JDC00, JDC10, JDC11, JDC20, JDC30, JDC40, JDC96, JDC97), respectively.

Ascertainment of outcome

The main outcome, pancreatic cancer, was ascertained through record linkage to the Cancer Register, which has used ICD-7 codes throughout the entire period of our study. Newly diagnosed cancers are mandatorily reported to the register by both clinicians and cytologists/pathologists with good quality (15), but patients without pathologic or cytologic confirmation are less likely to be reported (18). The Cause of Death Register, based on obligatory death certificates, thus reports more pancreatic cancer cases than the Cancer Register. We therefore ascertained pancreatic cancer not only in the Cancer Register (ICD-7, 157), but also through linkage to the Cause of Death Register (underlying cause of death, ICD-8/9, 157; ICD-10, C25). Patients with a prior history of pancreatic cancer were also excluded.

Other variables

In addition to age, sex, calendar year, and SNOMED codes obtained from the histopathology registers, we linked the cohort to the National Patient Register (19), to obtain information about occurrences of chronic pancreatitis (ICD-8, 577.10/577.19; ICD-9, 577B; ICD-10, K860/K861), cholelithiasis (ICD-8/9, 574; ICD-10, K80), and primary sclerosing cholangitis (ICD-8, 575.05; ICD-9, 576B; ICD-10, K830). These diagnoses have been implicated as risk factors of pancreatic cancer (20–22), but could also be associated with abdominal discomforts (23), which might lead to increased probability for gastroscopy (confounding by indications). Because the lag period from symptoms of chronic pancreatitis to diagnosis often lasts for a long time, we shifted the onset of chronic pancreatitis backward by 10 years (20). We also obtained information about diabetes (ICD-8/9, 250; ICD-10, E10-E14) and obesity (ICD-8, 277.99; ICD-9, 278A; ICD-10, E66). Patients were considered to have diabetes or obesity if the diagnosis records were before first biopsy. Chronic obstructive pulmonary disease (ICD-8/9, 491/492; ICD-10, J41-J44) and tobacco abuse (ICD-8, 989.9; ICD-9, 305B; ICD-10, F17/T65.2/Z71.6/Z72.0/Z864A) were treated as a proxy for smoking. Information on education levels was obtained from Education Register. Education level was classified as (i) low, if the highest schooling was primary education nine years and below; (ii) medium, if two or three years of secondary schooling; (iii) high, if postsecondary education and above; and (iv) unknown information. In addition, we ascertained family history of pancreatic cancer in this cohort by identifying all first-degree family members (parents, siblings, or children) through record linkage to the Swedish Multi-generation Register (24). Then this cohort of first-degree family members was linked to the Cancer Register and Cause of Death Register to capture pancreatic cancer cases.

Statistical analysis

Standardized incidence ratio (SIR, the ratio of the observed to expected number of pancreatic cancer cases) with 95% CI was calculated to estimate the excess risk in each biopsy group, compared with the Swedish general population. The expected number was calculated by multiplying the observed person-years with age- (5-year strata), sex-, and calendar year-specific incidence rates of pancreatic cancer in the Swedish general population. The denominator of these background incidence rates, that is, person-years at risk, was derived from the Swedish general population, and the numerator was derived from diagnoses in the Cancer Register and underlying cause of death in the Cause of Death Register. We calculated SIRs, stratified by follow-up time (0–1 year, 1–2 years, 2–3 years, 3–5 years, 5–10 years, and 10+ years after first biopsy). Cochran-Armitage trend test was used to evaluate time trends of the relative risks across follow-up time after the first 3 years. In addition, the distribution of patients diagnosed with pancreatic cancer in the first follow-up year was described by age, chronic pancreatitis, smoking-related diseases, obesity, and presence of family history of pancreatic cancer.

With regard to internal comparison within the levels of Correa's cascade, HRs from Cox proportional hazards regression model were used to evaluate the long-term association between gastric mucosal status and pancreatic cancer risk. In the Cox regression, we started follow-up after the first 3 years, to minimize selection bias. We used attained age as the underlying time scale, and adjusted for sex, age at baseline (<50 years, ≥50 and <60 years, ≥60 and <70 years, ≥70 and <80 years, ≥80 and ≤90 years), calendar year of baseline (1979–1990, 1991–2000, 2001–2011), chronic pancreatitis (no or yes), cholelithiasis (no or yes), primary sclerosing cholangitis (no or yes), diabetes (no or yes), obesity (no or yes), smoking-related diseases (no or yes),
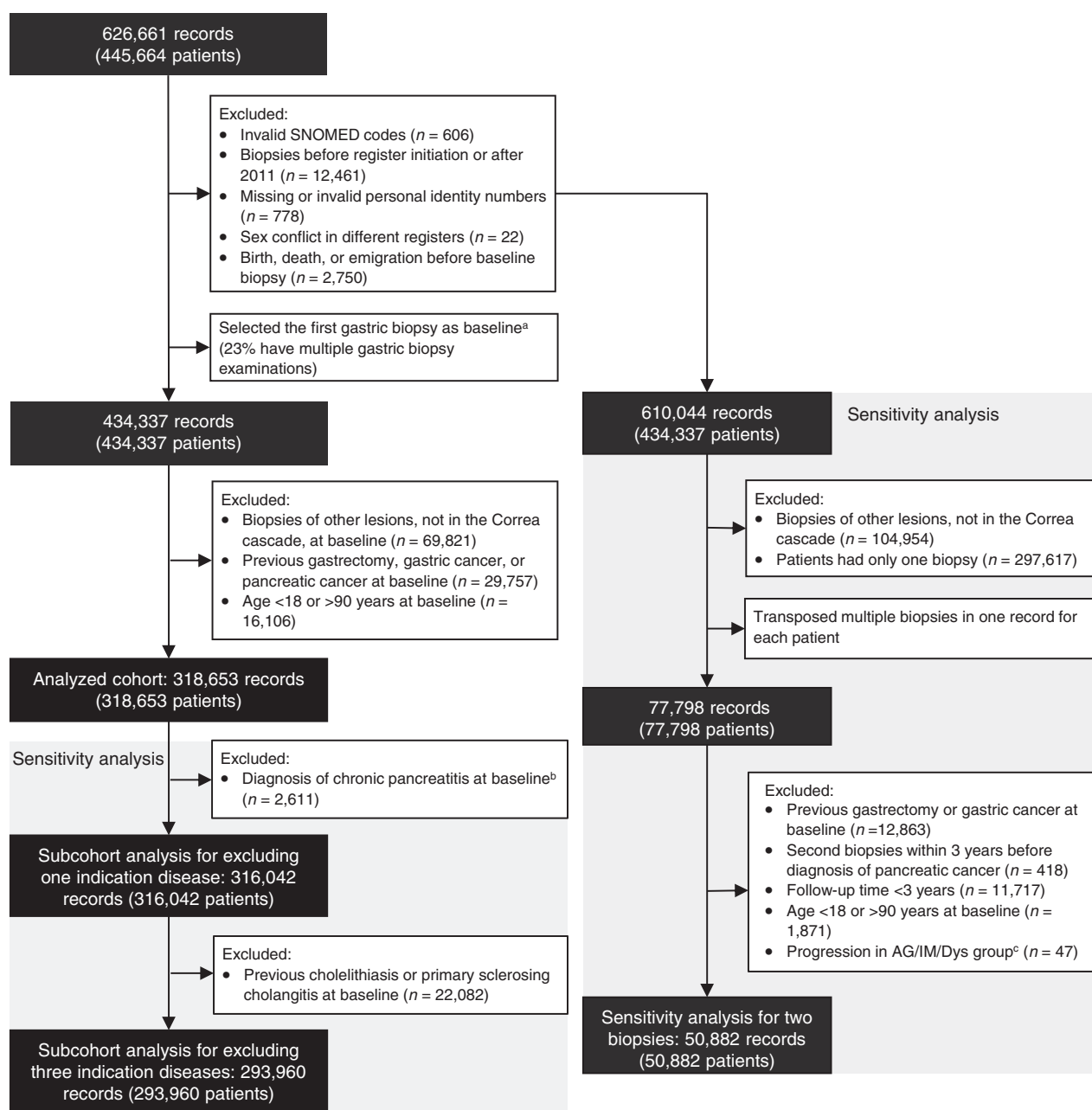
Figure 1.
Flowchart of the population-based gastric biopsy cohort in Sweden (1979–2014). [a]Baseline defined as first biopsy identified in the database. When multiple diagnoses were present, the most advanced one was selected. Codes for normal, minor changes, superficial gastritis, atrophic gastritis, intestinal metaplasia, dysplasia, and other lesions are listed in our previous study. [b]The onset of chronic pancreatitis was shifted backward by 10 years, and patients were defined as having chronic pancreatitis if the reported diagnosis of chronic pancreatitis with shifted onset at baseline. [c]Patients with AG/IM/Dys who progressed to more advanced lesions (gastric cancer) were excluded.

education level (low, medium, high, unknown), and family history of pancreatic cancer (no, yes, unknown), and stratified by pathology department. The proportional hazards assumption was checked by Schoenfeld residuals, and no indication of violation was observed.

We re-estimated SIRs with 95% CIs in two sensitivity analyses: first, we excluded patients with chronic pancreatitis, cholelithiasis, and primary sclerosing cholangitis to minimize potential confounding by indication. Second, we explored the effect of disease trajectory in

patients with two or more gastric biopsies: within each baseline group, those with more advanced lesions at the second biopsy (except gastric cancer) were classified as progressive, those with less advanced lesions at the second biopsy as regressive, and all others as stable. Biopsy records with examination dates within 3 years before diagnosis of pancreatic cancer were excluded to restrict indication bias.

All analyses were performed in SAS software Version 9.4 (SAS Institute). Two-sided $P < 0.05$ was considered statistically significant.

Results

We compiled 626,661 records relating to 445,664 patients who had undergone at least one gastric biopsy between 18 and 90 years old (**Fig. 1**). After data cleaning, 318,653 eligible patients remained in the analyzed cohort. Patients had median age of 61.2 years, and average follow-up of 10.8 years, accruing 3,438,248 person-years at risk (**Table 1**). Female patients were on average 1.5 years younger than men (58.4 vs. 59.8, $P < 0.001$). Female predominance was observed for all groups, from 52% (superficial gastritis) to 58% (normal), and patients with AG/IM/Dys had the shortest mean follow-up of 9.4 years.

Table 2 shows observed and expected pancreatic cancer cases, along with SIRs and 95% CIs, in different groups stratified by follow-up duration. During first, second, and third year of follow-up in AG/IM/Dys group, 177, 32, and 25 pancreatic cancer cases were observed, with SIR of 11.5 (95% CI, 9.9–13.4), 2.2 (95% CI, 1.5–3.1), and 1.8 (95% CI, 1.1–2.6), respectively. SIR was 1.3 (95% CI, 1.1–1.5) after the first 3 years of follow-up. Similar relative risk patterns were observed in other groups. SIRs during the first year of follow-up were 17.4 (95% CI, 15.7–19.3) for normal group, 20.8 (95% CI, 17.2–25.0) for minor changes, and 13.0 (95% CI, 12.2–13.8) for superficial gastritis; they dropped to 1.3 to 2.5 during the second and third year of follow-up. In sensitivity analyses by excluding patients with chronic pancreatitis, or further excluding those with cholelithiasis and primary sclerosing cholangitis, the SIRs remained constant or decreased slightly (Supplementary Table S1).

In the Cox regression with normal group as reference and a 3-year lag after first biopsy, adjusted HRs for pancreatic cancer were close to one for all exposure groups (minor changes: HR = 1.1, 95% CI, 0.8–1.4; superficial gastritis, HR = 1.0, 95% CI, 0.9–1.1; AG/IM/Dys, HR = 1.1, 95% CI, 0.9–1.3; all $P > 0.3$).

In the first year of follow-up, percentage of diagnosis for pancreatic cancer significantly increased with age, from 0.1% in 18 to 50 age group to 0.9% in 80 to 90 age group ($P_{trend} < 0.001$, **Table 3**). As expected, the corresponding percentage in patients with chronic pancreatitis was higher than those without chronic pancreatitis, the same as for family history of pancreatic cancer (Chi-square test, $P < 0.001$).

For patients who had at least two gastric biopsies, we performed further analyses by using mucosal change patterns with the first two biopsies (Supplementary Fig. S1). The SIR estimates for progressive strata were overall marginally larger than for the corresponding regressive, and stable strata within the same baseline group. We only found a statistically significant excess risk compared with the general population for the stable stratum in the AG/IM/Dys group at 1.9 (95% CI, 1.2–2.8).

Discussion

In our nationwide cohort study of participants with gastric biopsies, we found a high excess risk of pancreatic cancer shortly after first biopsy, especially during the first year of follow-up. Given similar excess risk for normal biopsies as well as across all stages of Correa's cascade, this is very likely driven by reverse causality and confounding by indications. From 3 years after the first biopsy, a 20% to 30% excess risk was observed for the members of this biopsy cohort when compared with the general population, again regardless of the gastric mucosal status. Taken together, we see no evidence for a long-term causal association between atrophic gastritis and more advanced precancerous lesions and the risk of pancreatic cancer.

Atrophic gastritis is characterized by gastric inflammation, loss of specialized glandular tissues in the gastric corpus, and consequent low gastric acid production (25, 26), sometimes also by the clearance of *H. pylori* colonization with advanced stages of atrophy (27). Low gastric acid (hypoacidity) subsequently appears to entail bacterial overgrowth and increase formation of N-nitroso compounds, which have been named as candidates for accelerating pancreatic carcinogenesis in both animals and humans (28, 29). A number of epidemiologic studies have also explored the association between gastric mucosal abnormality and pancreatic cancer risk. However, one meta-analysis conducted in 2017 could not confirm the association between atrophic gastritis and the risk of pancreatic cancer

Table 1. Characteristics of patients enrolled in the gastric biopsy cohort in Sweden.

Gastric biopsy at baseline[a]	No. of patients (n, %)	Age at entry (mean ± SD)	Follow-up years (mean ± SD)	Accumulated person-years
Overall				
Normal	84,778 (26.6)	51.9 ± 17.8	11.0 ± 6.4	930,938
Minor changes	14,266 (4.5)	60.7 ± 16.6	10.1 ± 7.5	144,548
Superficial gastritis	188,829 (59.3)	61.1 ± 16.5	11.0 ± 7.3	2,073,542
AG/IM/Dys	30,780 (9.6)	65.5 ± 15.1	9.4 ± 6.5	289,220
Total	318,653 (100)	59.1 ± 17.3	10.8 ± 7.0	3,438,248
Men				
Normal	34,692 (23.9)	53.2 ± 17.2	10.7 ± 6.7	370,459
Minor changes	6,441 (4.4)	60.8 ± 15.9	9.7 ± 7.5	62,466
Superficial gastritis	89,700 (61.9)	61.3 ± 15.8	10.7 ± 7.5	960,257
AG/IM/Dys	14,252 (9.8)	66.5 ± 13.9	8.8 ± 6.5	125,100
Total	145,085 (100)	59.8 ± 16.5	10.5 ± 7.2	1,518,282
Women				
Normal	50,086 (28.9)	51.0 ± 18.1	11.2 ± 6.3	560,478
Minor changes	7,825 (4.5)	60.7 ± 17.1	10.5 ± 7.5	82,082
Superficial gastritis	99,129 (57.1)	61.0 ± 17.1	11.2 ± 7.1	1,113,286
AG/IM/Dys	16,528 (9.5)	64.7 ± 16.1	9.9 ± 6.5	164,120
Total	173,568 (100)	58.4 ± 18.0	11.1 ± 6.9	1,919,966

[a]Gastric biopsy at baseline was defined as first biopsy examination identified in the database. When multiple diagnoses were present, the most advanced one was selected.

Table 2. SIRs with 95% CIs for pancreatic cancer by follow-up time, in the gastric biopsy cohort in Sweden.

Follow-up years in biopsy groups	O (E)	SIR (95% CI)
Normal		
0–1	373 (21.4)	17.4 (15.7–19.3)***
1–2	46 (21.3)	2.2 (1.6–2.9)***
2–3	28 (21.5)	1.3 (0.9–1.9)
3+	296 (246.2)	1.2 (1.1–1.4)**
3–5	49 (43.0)	1.1 (0.8–1.5)
5–10	104 (91.3)	1.1 (0.9–1.4)
10+	143 (111.9)	1.3 (1.1–1.5)**
P_{trend}		0.534
Minor changes		
0–1	116 (5.6)	20.8 (17.2–25.0)***
1–2	9 (5.3)	1.7 (0.8–3.2)
2–3	13 (5.1)	2.5 (1.3–4.3)**
3+	65 (51.6)	1.3 (1.0–1.6)
3–5	13 (9.7)	1.3 (0.7–2.3)
5–10	27 (19.3)	1.4 (0.9–2.0)
10+	25 (22.6)	1.1 (0.7–1.6)
P_{trend}		0.638
Superficial gastritis		
0–1	1,004 (77.2)	13.0 (12.2–13.8)***
1–2	141 (74.3)	1.9 (1.6–2.2)***
2–3	96 (72.9)	1.3 (1.1–1.6)*
3+	958 (821.8)	1.2 (1.1–1.2)***
3–5	161 (139.6)	1.2 (1.0–1.3)
5–10	336 (293.9)	1.1 (1.0–1.3)*
10+	461 (388.1)	1.2 (1.1–1.3) ***
P_{trend}		0.788
AG/IM/Dys		
0–1	177 (15.3)	11.5 (9.9–13.4)***
1–2	32 (14.7)	2.2 (1.5–3.1)***
2–3	25 (14.3)	1.8 (1.1–2.6)*
3+	161 (126.4)	1.3 (1.1–1.5)**
3–5	34 (27.1)	1.3 (0.9–1.8)
5–10	69 (50.6)	1.4 (1.1–1.7)*
10+	58 (48.8)	1.2 (0.9–1.5)
P_{trend}		0.791

Abbreviations: E, expected number of outcome; O, observed number of outcome. P_{trend}, Cochran–Armitage trend test after the first 3 years of follow-up.
*, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$.

(5). One recent prospective cohort study in Japan, in which atrophic gastritis was diagnosed serologically, reported a significant positive association only among current smokers (6). Another cohort study conducted among male smokers in Finland found no statistically significant positive association between atrophic gastritis (whether serologic or histologic) and pancreatic cancer risk, with the normal serum pepsinogen I (≥25 μg/L) as reference (30).

In our present study, biopsied patients had a 12- to 21-fold risk of pancreatic cancer compared with the Swedish general population (matched by age, sex, and calendar year) within the first year of follow-up. Thereafter, the relative risk decreased substantially. This short-term association can have several explanations. It may be due to enhanced surveillance of patients with gastroscopy, which increases the probability of discovering as yet patients with undiagnosed pancreatic cancer. Moreover, some typical indications are inherent in the decision for having gastroscopy and may also be related to pancreatic cancer risk (confounding by indications). These indications, including upper abdominal pain or discomforts, nausea,

vomiting, etc., sometimes cannot be resolved by initial physical exam or blood test. Previous studies suggested that some disorders, including dyspepsia, gastroesophageal reflux disease, peptic ulcer disease with *H. pylori* infection, diabetes, cholelithiasis, chronic pancreatitis, inflammatory bowel disease, and other gastrointestinal cancers, have the same underlying symptoms and therefore lead to upper gastrointestinal endoscopy and/or biopsy samplings (23, 31, 32). Some of these disorders have also been reported to associate with an increased risk of pancreatic cancer (22, 33–36).

When investigating pancreatic cancer cases during the first year after baseline biopsy, we found that about 9 in 1,000 patients older than 70 years, and 8 in 1,000 patients with family history of pancreatic cancer were diagnosed with pancreatic cancer, and the percentage was higher in patients with chronic pancreatitis (17/1,000). These results from an unselected patient group, representing the combined experience over many years in a whole country may serve to develop a guideline for clinicians when advising patients for further investigation. However, future studies are needed to confirm our findings.

A 20% to 30% increased risk of pancreatic cancer was observed for all stages of Correa's cascade (except gastric cancer) of biopsied patients after the first 3 years of follow-up, when compared with the Swedish general population. After excluding some possible indications to minimize confounding effects (chronic pancreatitis, cholelithiasis, and primary sclerosing cholangitis), a 10% to 20% increased risk was still observed. However, the magnitude of long-term risk was the same across all groups, including the normal mucosal group, which strongly suggests that it is not the differences along the Correa's cascade that drive the excess risk compared with the general population. This is supported by the results from the Cox regression, which did not present increased risk of pancreatic cancer compared with the normal mucosal group. Some patients may receive gastroscopy not due to any gastric disorder, but disorders in other organs with similar indications, such as new-onset diabetes, while still increasing the risk of pancreatic cancer, or may already have existing cancer, given the insidious onset and nonspecific symptoms in early stages. Furthermore, the biopsy only focuses on the target sampling areas of stomach and has no microscopic information of the mucosa that has normal endoscopic appearance.

To the best of our knowledge, this is the largest follow-up study to investigate the association between gastric mucosal status and pancreatic cancer risk by using the "gold standard"—histologic diagnosis of gastric mucosa. In most epidemiologic studies, serum pepsinogen I and pepsinogen I/II ratio have been used for diagnosis of atrophic gastritis—however, these markers are affected by demographic characteristics and dietary habits, as well as cut-off points of pepsinogens. It is possible that the difference in pepsinogen cut-offs used to define atrophic gastritis between countries may cause variations in the findings. Therefore, using the most advanced lesion of gastric mucosa observed in histopathology as the exposure is likely to be more accurate, although biopsy sampling error, number of biopsies, and inter- or intraobserver variation in diagnoses may exist. To be noted, some studies focused on the exposure of *H. pylori* infection, a trigger of Correa's cascade, and its association with pancreatic cancer risk. Glandular cell loss, low gastric acid environment, and subsequent non-*H. pylori* microorganisms' overgrowth can shift *H. pylori* colonization in the gastric mucosa, especially after glandular atrophy (25, 37). Therefore, the presence or absence of *H. pylori* cannot consistently reflect the accurate pathophysiologic changes of the stomach. Furthermore, due to the structure of the Swedish healthcare system, our cohort included virtually all patients who underwent gastroscopy with biopsies in Sweden (13). High-quality linkage

Table 3. Percentage of diagnosis of pancreatic cancer during the first year of follow-up in the gastric biopsy cohort in Sweden.

Parameters	Overall			Men			Women		
	No. of patients	Percentage of pancreatic cancer (%)	P value[a]	No. of patients	Percentage of pancreatic cancer (%)	P value[a]	No. of patients	Percentage of pancreatic cancer (%)	P value[a]
Age at baseline			<0.001***[b]			<0.001***[b]			<0.001***[b]
≥18 and <50	94,356	0.1		39,246	0.1		55,110	0	
≥50 and <60	57,397	0.4		27,173	0.5		30,224	0.2	
≥60 and <70	64,800	0.7		32,156	0.8		32,644	0.5	
≥70 and <80	68,087	0.9		32,197	1.1		35,890	0.8	
≥80 and ≤90	34,013	0.9		14,313	1.1		19,700	0.8	
Chronic pancreatitis[c]			<0.001***			<0.001***			<0.001***
No	316,288	0.5		143,577	0.6		172,711	0.4	
Yes	2,365	1.7		1,508	1.7		857	1.8	
Smoking-related diseases[d]			0.188			0.296			0.653
No	310,013	0.5		140,623	0.7		169,390	0.4	
Yes	8,640	0.6		4,462	0.8		4,178	0.5	
Obesity			0.020*			0.251			0.083
No	315,012	0.5		144,021	0.7		170,991	0.4	
Yes	3,641	0.2		1,064	0.4		2,577	0.2	
Family history			<0.001***			<0.001***			<0.001***
No	277,818	0.5		125,440	0.6		152,378	0.4	
Yes	5,339	0.8		2,431	1.0		2,908	0.7	
One relative-child	800	1.4		346	1.7		454	1.1	
One relative-parent	3,466	0.6		1,580	0.8		1,886	0.4	
One relative-sibling	941	1.2		447	1.3		494	1.0	
More than one relative	132	1.5		58	1.7		74	1.4	
Unknown	35,496	0.8		17,214	0.8		18,282	0.7	

[a]P value was derived from Chi-square test.
[b]P value was derived from Cochran–Armitage trend test.
[c]The onset of chronic pancreatitis was shifted backward by 10 years, and patients were defined as having chronic pancreatitis if the reported diagnosis of chronic pancreatitis with shifted onset at baseline.
[d]Smoking-related diseases, diagnoses of chronic obstructive pulmonary disease and tobacco abuse, at or before baseline.
*, P < 0.05; **, P < 0.01; ***, P < 0.001.

between this biopsy cohort and other national registers with high quality allowed us to follow cancer outcomes as well as censoring events over a long period.

Limitations to be highlighted include the fact that patients in our gastric biopsy cohort were not randomly sampled from the general population, but underwent gastroscopy with biopsy samplings due to clinical indications. Consequently, our findings are based on comparing risk of pancreatic cancer among patients at different levels of Correa's cascade in a clinically worked-up cohort and cannot be readily generalized to healthy people who did not undergo gastroscopy. Furthermore, we cannot identify cases of autoimmune gastritis, which consequently would be classified as AG/Dys/IM. However, the epidemiology of autoimmune gastritis and its association with nongastric cancers are still mostly unknown, and some studies in comparable settings of enrolment (i.e., histological assessment in patients undergoing gastroscopy due to clinical indications) report a prevalence of 2% to 3% (38, 39). It suggests that the potential misclassification of exposure in our study is likely limited (40). In addition, we did not have information on an important indication—new-onset diabetes. It has common gastrointestinal symptoms, where the upper gastrointestinal endoscopy is usually used to exclude physiologic or pathologic disorders (32); at the same time, it is a risk factor of pancreatic cancer (OR = 6.4; 95% CI, 4.2–9.8; ref. 36). Finally, like other register-based studies, we lacked exact information of risk factors for pancreatic cancer in this cohort, such as environmental or lifestyle exposures, which might be useful for further adjustments.

Conclusions

This unique large pathologic cohort study did not find evidence that atrophic gastritis or more advanced precancerous lesions are causally associated with an increased risk of pancreatic cancer. A highly increased short-term risk of pancreatic cancer observed for people undergoing gastroscopy with biopsy sampling is likely due to reverse causality and confounding by indications.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding authors. The data are not publicly available due to privacy or ethical restrictions.

Ethical Considerations

Ethical approval for this study was granted by the Regional Ethical Review Board in Stockholm (Dnr 2010/819–31/3; 2013/1244–32; 2015/1469–32; 2016/247–32; 2016/525–32).

What this Study Adds?

- To the best of our knowledge, this is the first nationwide biopsy cohort study concerning gastric mucosal abnormality (atrophic gastritis and more advanced precancerous lesions) and its association with pancreatic cancer risk.
- Our results do not provide evidence that gastric precancerous lesions are causally associated with pancreatic cancer risk (long-term).

• An increased risk was observed within three years (short-term) for people seeking gastroscopy.

Authors' Disclosures

No author disclosures were reported.

Authors' Contributions

J. Yu: Conceptualization, data curation, software, formal analysis, visualization, methodology, writing–original draft, writing–review and editing. **H. Song:** Data curation, formal analysis, writing–review and editing. **I. Ekheden:** Resources, data curation. **M. Löhr:** Writing–review and editing. **A. Ploner:** Formal analysis, methodology, writing–review and editing, interpretation of the data. **W. Ye:** Conceptualization, resources, supervision, funding acquisition, methodology, writing–review and editing.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69: 7–34.
2. Moyer MT, Gaffney RR. Pancreatic adenocarcinoma. N Engl J Med 2014;371: 2140.
3. Kamisawa T, Wood LD, Itoi T, Takaori K. Pancreatic cancer. Lancet 2016;388: 73–85.
4. Barone E, Corrado A, Gemignani F, Landi S. Environmental risk factors for pancreatic cancer: an update. Arch Toxicol 2016;90:2617–42.
5. Liu H, Chen YT, Wang R, Chen XZ. Helicobacter pylori infection, atrophic gastritis, and pancreatic cancer risk: a meta-analysis of prospective epidemiologic studies. Medicine (Baltimore) 2017;96:e7811.
6. Hirabayashi M, Inoue M, Sawada N, Saito E, Abe SK, Hidaka A, et al. Helicobacter pylori infection, atrophic gastritis, and risk of pancreatic cancer: a population-based cohort study in a large Japanese population: the JPHC Study. Sci Rep 2019; 9:6099.
7. Maisonneuve P, Lowenfels AB. Risk factors for pancreatic cancer: a summary review of meta-analytical studies. Int J Epidemiol 2015;44:186–98.
8. Kumar S, Metz DC, Kaplan DE, Goldberg DS. The association of Helicobacter pylori with pancreatic cancer. GastroHep 2020;2:157–64.
9. Hooi JKY, Lai WY, Ng WK, Suen MMY, Underwood FE, Tanyingoh D, et al. Global prevalence of Helicobacter pylori infection: systematic review and meta-analysis. Gastroenterology 2017;153:420–9.
10. Correa P, Piazuelo MB. The gastric precancerous cascade. J Dig Dis 2012;13:2–9.
11. Kapadia CR. Gastric atrophy, metaplasia, and dysplasia: a clinical perspective. J Clin Gastroenterol 2003;36:S29–36; discussion S61-2.
12. Huang J, Zagai U, Hallmans G, Nyren O, Engstrand L, Stolzenberg-Solomon R, et al. Helicobacter pylori infection, chronic corpus atrophic gastritis and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort: a nested case-control study. Int J Cancer 2017;140: 1727–35.
13. Song H, Ekheden IG, Zheng Z, Ericsson J, Nyren O, Ye W. Incidence of gastric cancer among patients with gastric precancerous lesions: observational cohort study in a low risk Western population. BMJ 2015;351:h3867.
14. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur J Epidemiol 2009;24:659–67.
15. Barlow L, Westergren K, Holmberg L, Talback M. The completeness of the Swedish Cancer Register: a sample survey for year 1998. Acta Oncol 2009;48: 27–33.
16. Brooke HL, Talback M, Hornblad J, Johansson LA, Ludvigsson JF, Druid H, et al. The Swedish cause of death register. Eur J Epidemiol 2017;32:765–73.
17. Ludvigsson JF, Almqvist C, Bonamy AK, Ljung R, Michaelsson K, Neovius M, et al. Registers of the Swedish total population and their use in medical research. Eur J Epidemiol 2016;31:125–36.
18. Kilander C, Mattsson F, Ljung R, Lagergren J, Sadr-Azodi O. Systematic underreporting of the population-based incidence of pancreatic and biliary tract cancers. Acta Oncol 2014;53:822–9.
19. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health 2011;11:450.
20. Kirkegard J, Mortensen FV, Cronin-Fenton D. Chronic pancreatitis and pancreatic cancer risk: a systematic review and meta-analysis. Am J Gastroenterol 2017;1:218.
21. Søgaard KK, Erichsen R, Lund JL, Farkas DK, Sørensen HT. Cholangitis and subsequent gastrointestinal cancer risk: a Danish population-based cohort study. Gut 2014;63:356–61.
22. Fan Y, Hu J, Feng B, Wang W, Yao G, Zhai J, et al. Increased risk of pancreatic cancer related to gallstones and cholecystectomy: a systematic review and meta-analysis. Pancreas 2016;45:503–9.
23. Talley NJ, Ford AC. Functional dyspepsia. N Engl J Med 2015;373:1853–63.
24. Ekbom A. The Swedish multi-generation register. Methods Mol Biol 2011;675: 215–20.
25. Fox JG, Wang TC. Inflammation, atrophy, and gastric cancer. J Clin Invest 2007; 117:60–9.
26. Waldum HL, Kleveland PM, Sordal OF. Helicobacter pylori and gastric acid: an intimate and reciprocal relationship. Therap Adv Gastroenterol 2016;9: 836–44.
27. Weck MN, Gao L, Brenner H. Helicobacter pylori infection and chronic atrophic gastritis: associations according to severity of disease. Epidemiology 2009;20: 569–74.
28. Kokkinakis DM, Subbarao V. The significance of DNA damage, its repair and cell proliferation during carcinogen treatment in the initiation of pancreatic cancer in the hamster model. Cancer Res 1993;53:2790–5.
29. Risch HA. Etiology of pancreatic cancer, with a hypothesis concerning the role of N-nitroso compounds and excess gastric acidity. J Natl Cancer Inst 2003;95:948–60.
30. Laiyemo AO, Kamangar F, Marcus PM, Taylor PR, Virtamo J, Albanes D, et al. Serum pepsinogen level, atrophic gastritis and the risk of incident pancreatic cancer–a prospective cohort study. Cancer Epidemiol 2009;33: 368–73.
31. Allen JI, Katzka D, Robert M, Leontiadis GI. American Gastroenterological Association Institute technical review on the role of upper gastrointestinal biopsy to evaluate dyspepsia in the adult patient in the absence of visible mucosal lesions. Gastroenterology 2015;149:1088–118.
32. Du YT, Rayner CK, Jones KL, Talley NJ, Horowitz M. Gastrointestinal symptoms in diabetes: prevalence, assessment, pathogenesis, and management. Diabetes Care 2018;41:627–37.
33. Luo J, Nordenvall C, Nyren O, Adami HO, Permert J, Ye W. The risk of pancreatic cancer in patients with gastric or duodenal ulcer disease. Int J Cancer 2007;120:368–72.
34. Raimondi S, Lowenfels AB, Morselli-Labate AM, Maisonneuve P, Pezzilli R. Pancreatic cancer in chronic pancreatitis; aetiology, incidence, and early detection. Best Pract Res Clin Gastroenterol 2010;24:349–58.
35. Everhov ÅH, Erichsen R, Sachs MC, Pedersen L, Halfvarson J, Askling J, et al. Inflammatory bowel disease and pancreatic cancer: a Scandinavian register-based cohort study 1969–2017. Aliment Pharmacol Ther 2020;52:143–54.
36. Molina-Montes E, Coscia C, Gómez-Rubio P, Fernández A, Boenink R, Rava M, et al. Deciphering the complex interplay between pancreatic cancer, diabetes mellitus subtypes and obesity/BMI through causal inference and mediation analyses. Gut 2021;70:319–29.

37. Zhang C, Yamada N, Wu YL, Wen M, Matsuhisa T, Matsukura N. Comparison of *Helicobacter pylori* infection and gastric mucosal histological features of gastric ulcer patients with chronic gastritis patients. World J Gastroenterol 2005;11:976–81.

38. Zhang H, Jin Z, Cui R, Ding S, Huang Y, Zhou L. Autoimmune metaplastic atrophic gastritis in chinese: a study of 320 patients at a large tertiary medical center. Scand J Gastroenterol 2017;52:150–6.

39. Wolf EM, Plieschnegger W, Geppert M, Wigginghaus B, Höss GM, Eherer A, et al. Changing prevalence patterns in endoscopic and histological diagnosis of gastritis? Data from a cross-sectional Central European multicentre study. Dig Liver Dis 2014;46: 412–8.

40. Lenti MV, Rugge M, Lahner E, Miceli E, Toh BH, Genta RM, et al. Autoimmune gastritis. Nat Rev Dis Primers 2020;6:56.