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Long-Term Risk of Gastric Cancer by Subsite in Operated and Unoperated Patients Hospitalized for Peptic Ulcer

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OBJECTIVE: We aimed to investigate whether the elevated risk of gastric cancer among patients with gastric ulcer (GU) and the enigmatic low risk among patients with duodenal ulcer (DU) pertain to both cardia and noncardia cancer. We also studied the risks among operated patients while taking the disparate baseline risks into consideration.

METHODS: Retrospective cohorts of 59,550 and 79,412 unoperated patients with DU and GU, respectively, plus 12,840 patients with partial gastric resection and 8,105 with vagotomy, recorded in the Swedish Inpatient Register since 1970, were followed from the first hospitalization (date of operation for the surgery cohort) until occurrence of any cancer, death, emigration, definitive surgery, or December 31, 2003. Standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) expressed relative risk (RR), compared to the age-, sex-, and calendar period-matched Swedish population. Cox regression produced adjusted RR estimates among operated patients, relative to unoperated ones with the same ulcer type.

RESULTS: While unoperated DU patients had a halved risk of noncardia cancer (SIR = 0.5, 95% CI 0.4–0.7), their risk of cardia cancer was slightly above expectation (SIR = 1.2, 95% CI 0.8–1.7). Unoperated GU patients had doubled risks for both cancers (SIR = 2.1, 95% CI 2.0–2.4 and SIR = 1.9, 95% CI 1.4–2.3, respectively). DU patients who underwent gastric resection had a 60% risk elevation (RR = 1.6, 95% CI 1.0–2.5) compared to unoperated ones. Vagotomy was associated with a greater risk in the first 10 yr, but this excess disappeared with further follow-up. Resected GU patients had a 40% risk reduction relative to their unoperated peers (RR = 0.6, 95% CI 0.5–0.8). This reduction persisted well beyond the first postoperative decade.

CONCLUSION: The DU-related protection against gastric cancer does not seem to pertain to cardia cancer. With gastric resection, risks are shifted toward normality, regardless of underlying ulcer type.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a well-established cause of peptic ulcer disease (1, 2). It appears that the clinical outcome of the infection is linked to the pattern of colonization; those with an antrum-predominant infection tend to have less efficient control of acid production, leading to hyperacidity (3), and the development of duodenal ulcer (DU) in some (4). In contrast, *H. pylori* colonizes both the antrum and corpus in other hosts. Corpus-predominant gastritis, further inhibition of acid secretion from the corpus parietal cells, and gastric ulcer (GU) formation tend to follow down the line.

We have previously reported that while patients hospitalized for GU, as expected, have a greater risk of gastric cancer, those with DU have a low risk (5), despite the strong overall association between *H. pylori* seropositivity and noncardia gastric cancer risk (6–9), and the fact that approximately 90% of duodenal ulcer patients are infected. This observation points to the possibility of important effect modification of the *H. pylori*–gastric cancer relationship, conceivably by specific strain characteristics, host predisposition, external or intragastric environment, or any combination of these factors. Due to limited sample size and relatively short follow-up, analyses by anatomic subsite of stomach cancer were not possible in our previous study. Moreover, since artificially induced hypoacidity could theoretically be conducive to *H. pylori* colonization of the gastric corpus—in turn a conceivable risk factor for noncardia gastric cancer—studies of the long-term outcome among vagotomized patients are clearly warranted.

In this large retrospective cohort study, we have expanded our previous cohort (5) and extended follow-up considerably, thus permitting a thorough exploration of gastric cancer risk by anatomical subsite among unoperated patients hospitalized for DU or GU. Furthermore, although studied previously (10–19), owing to the accumulation of person-time among

operated patients, this study offers an unprecedented opportunity to study gastric cancer risk with reasonable precision among vagotomized patients and those who underwent partial gastric resection while taking the disparate baseline risks into consideration.

MATERIAL AND METHODS

The Cohort

The methodology used in this register-based retrospective cohort study has been detailed previously (5). Briefly, all patients in the Swedish Inpatient Register (20) with a diagnosis of DU (International Classification of Disease [ICD-7] code 541, ICD-8 and ICD-9 code 532, and ICD-10 code K26) or GU (ICD-7 code 540, ICD-8 and ICD-9 code 531, and ICD-10 code K25) were considered for inclusion in the cohort. We did not include individuals who were registered with both types of ulcer. For each potential subject, we identified the index episode—the first recorded hospitalization for the ulcer.

For each of the potentially eligible subjects, the national registration number (NRN, individually unique personal identifiers assigned to all Swedish residents and used in all of the registries used in this study) was checked in nationwide registers of total population, emigration, and death. Records with NRNs that could not be located in any of these registers (N = 4,536) were regarded as invalid and excluded. We further excluded 22,851 patients with diagnoses of any cancer before or at the time of the index episode, 12,232 individuals who died during the index hospitalization, and 1,912 records due to inconsistencies revealed during data editing and record linkages. Finally, our study included 176,017 individuals for further analysis.

Follow-Up

We linked the national registration numbers to the nationwide registries of migration and cause of death to obtain information on dates of emigration and death. The national Swedish Cancer Registry, established in 1958 and reportedly more than 98% complete (21), was used to identify all cancer cases in the cohort. We only considered first cancers and disregarded benign tumors or cancers found incidentally at autopsy. The patients in the unoperated cohort were followed up from the date of their first hospital admission for DU or GU until the date of emigration, death, gastric resection, vagotomy, a diagnosis of any cancer, or until December 31, 2003, whichever occurred first. However, person-time accrued and cancer events observed during the first year of follow-up was not counted in the analyses, since prodromal cancer symptoms are likely to increase the probability of hospitalization for any known prevalent disease, including peptic ulcer, leading to selection bias in the first year. Further, cancers that are mistaken for benign ulcers will artificially influence the cancer rates in the first year.

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

Statistical Analysis

The standardized incidence ratio (SIR)—the ratio of the observed to the expected number of cancers in the cohort—was used as a measure of relative risk (RR). The expected number of cancers was calculated by adding up all person-time experienced in the cohort divided into strata of sex, age (in 5-yr groups), and calendar year of observation (aggregated into 5-yr intervals) and then multiplying the stratum-specific person-time by the corresponding stratum-specific incidence rates obtained in the entire Swedish population. In the calculation of these incidence rates, the denominator was estimated by the number of mid-year population without a previously reported cancer. The 95% confidence intervals (CIs) for the SIRs were calculated assuming that the observed events followed a Poisson distribution (22). We further performed stratified analyses by follow-up duration, sex, presence of complications (bleeding or perforation) at the time of hospitalization, calendar period of index hospitalization (before *vs* after 1980), age at entry ($<$50, 50–69, 70+), and the calendar period of follow-up (before *vs* after 1990).

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

All statistical analyses were performed with SAS, release 8.2 (SAS Institute, Cary, NC); PROC PHREG was used for the regression model. All statistical tests were 2-sided.

RESULTS

The final cohort included 59,550 unoperated patients with DU (64.2% male), 79,412 unoperated patients with GU (52.3% male), 12,840 patients with partial gastric resection (59.0% male), and 8,105 patients with vagotomy (69.8% male). Patients who underwent surgical treatment were younger than unoperated patients and followed for longer time. About half of the peptic ulcer patients were hospitalized due to bleeding and about 10% due to perforation. Some characteristics of the patients are given in Table 1.

Duodenal Ulcers

Among the 59,550 unoperated patients with DU followed for an average of 8.8 yr, 36 cardia cancer cases were diagnosed

Table 1. Characteristics of Patients Hospitalized for Peptic Ulcer in Sweden 1970–2003

Characteristic	Duodenal Ulcers	Gastric Ulcers	Partial Gastric Resection			Vagotomy
			Billroth I	Billroth II	All	
Number of patients	59,550	79,412	6,639	5,407	12,840	8,105
Male (%)	64.2	52.3	49.3	71.4	59.0	69.8
Age at index hospitalization, (%)						
<40 yr	11.8	6.1	12.7	10.7	11.6	29.0
40–49 yr	11.7	8.3	20.2	16.1	17.9	25.2
50–59 yr	15.9	14.1	28.0	26.1	26.8	24.2
60–69 yr	19.8	20.3	23.7	25.7	24.7	13.3
70–79 yr	24.3	29.2	13.2	17.7	15.7	6.4
≥80 yr	16.5	22.0	2.3	3.8	3.4	1.9
Mean (yr)	62.4	66.9	55.3	57.7	56.7	48.4
Reason for index hospitalization, (%)						
Bleeding	49	47	38	51	44	32
Perforation	9	9	6	10	9	6
Other	42	44	56	39	47	62
Total person-year of follow-up	494,577	552,736	105,935	74,856	189,777	138,814
Average follow-up time, yr	8.8	7.0	16	14	14.9	17.3
Mean age at cancer diagnosis, yr						
Gastric cardia cancer	69	74	68	70	69	70
Gastric noncardia cancer	73	73	70	69	69	65

after the first year of follow-up (SIR = 1.2, 95% CI 0.8–1.7) (Table 2). Stratified analyses of SIR for cardia cancer were essentially uninformative due to small numbers of observed cases in substrata. Noncardia gastric cancer was diagnosed less often than expected (N = 94, SIR = 0.5, 95% CI 0.4–0.7). The low RR was seen in virtually all investigated substrata, but it appeared to be more marked among men than among women, where the point estimate was no more than 20% below unity and nonsignificant (Table 2).

Gastric Ulcers

Following 79,412 unoperated patients with GU for an average of 7.0 yr, a higher than expected incidence of gastric cardia cancer emerged (N = 65, SIR = 1.9, 95% CI 1.4–2.3) (Table 3). No conspicuous variation in RR of cardia cancer was observed in stratified analyses by follow-up duration, sex, complication history, calendar year, or age at entry, although only one case was observed among patients less than 50 yr of age. During the same follow-up, 462 noncardia gastric cancers were registered (SIR = 2.1, 95% CI 2.0–2.4). The relative excess tended to be higher among patients entering the cohort in the early part of the study period, and among those who belonged to the younger age strata at entry.

Surgical Treatment

Table 4 shows the adjusted RRs (hazards) of developing noncardia cancer among operated ulcer patients, relative to unoperated patients with the same ulcer type (internal comparison). These RRs were estimated with Cox proportional hazards regression modeling. For comparison, SIR values, *i.e.*, the RRs in each subcategory relative to the age-, sex-, and calendar period-matched general population, are shown in the rightmost column. The results for cardia cancer were essentially uninformative due to small numbers of observed cases in the exposed groups. For the same reason, we do not report RRs of noncardia cancer among vagotomized GU patients.

Overall, operated patients with DU remained at a risk of noncardia gastric cancer that was below the risk in the matching general population (SIR = 0.8, 95% CI 0.5–1.2 among partially resected and SIR = 0.8, 95% CI 0.5–1.3 among

Table 2. Standardized Incidence Ratios (SIRs) and Their 95% Confidence Intervals (CIs) for Gastric Cancer by Subsite Among Nonoperated Patients With Duodenal Ulcer, by Follow-Up Duration, Sex, Presence of Complication, and Calendar Year of Index Hospitalization*

	Cardia Cancer		Noncardia Cancer	
	No. of Cases	SIR (95% CI)	No. of Cases	SIR (95% CI)
Overall	36	1.2 (0.8–1.7)	94	0.5 (0.4–0.7)
Follow-up year				
2–10	27	1.4 (0.95–2.1)	70	0.6 (0.5–0.7)
11+	9	0.8 (0.4–1.5)	24	0.5 (0.3–0.7)
Sex				
Men	32	1.3 (0.9–1.8)	61	0.5 (0.4–0.6)
Women	4	0.9 (0.3–2.4)	33	0.8 (0.5–1.1)
Complication†				
Yes	20	1.0 (0.6–1.6)	60	0.5 (0.4–0.7)
No	16	1.5 (0.9–2.4)	34	0.6 (0.4–0.8)
Calendar year of index hospitalization				
1970–1979	6	0.6 (0.2–1.3)	45	0.6 (0.5–0.8)
1980–2003	30	1.5 (1.01–2.1)	49	0.5 (0.4–0.7)
Age at entry				
<50	7	1.8 (0.7–3.7)	13	1.0 (0.5–1.7)
50–69	20	1.3 (0.8–2.0)	41	0.5 (0.4–0.7)
70+	9	0.8 (0.4–1.6)	40	0.5 (0.4–0.7)
Calendar year of follow-up				
<1990	8	0.9 (0.4–1.9)	48	0.6 (0.5–0.8)
≥1990	28	1.3 (0.9–1.9)	46	0.5 (0.4–0.7)

*First year of follow-up excluded.
†Including bleeding and perforation.

Table 3. Standardized Incidence Ratios (SIRs) and Their 95% Confidence Intervals (CIs) for Gastric Cancer by Subsite Among Nonoperated Patients With Gastric Ulcer, by Follow-Up Duration, Sex, Presence of Complication, and Calendar Year of Index Hospitalization*

	Cardia Cancer		Noncardia Cancer	
	No. of Cases	SIR (95% CI)	No. of Cases	SIR (95% CI)
Overall	65	1.9 (1.5–2.5)	462	2.1 (2.0–2.4)
Follow-up year				
2–10	49	2.1 (1.6–2.8)	350	2.2 (1.9–2.4)
11+	16	1.6 (0.9–2.5)	112	2.1 (1.7–2.5)
Sex				
Men	52	2.0 (1.5–2.6)	284	2.1 (1.8–2.3)
Women	13	1.7 (0.9–2.9)	178	2.3 (2.0–2.6)
Complication†				
Yes	39	1.9 (1.4–2.6)	284	2.2 (2.0–2.4)
No	26	2.0 (1.3–2.9)	178	2.1 (1.8–2.4)
Calendar year of index hospitalization				
1970–1979	21	2.2 (1.4–3.4)	200	2.4 (2.1–2.8)
1980–2003	44	1.8 (1.3–2.5)	262	2.0 (1.8–2.2)
Age at entry				
<50	1	0.4 (0.01–2.0)	54	5.4 (4.1–7.1)
50–69	40	2.5 (1.8–3.4)	204	2.3 (2.0–2.6)
70+	24	1.6 (1.1–2.5)	204	1.8 (1.5–2.0)
Calendar year of follow-up				
<1990	26	2.6 (1.7–3.8)	237	2.3 (2.1–2.7)
≥1990	39	1.7 (1.2–2.3)	225	2.0 (1.7–2.2)

*First year of follow-up excluded.
†Including bleeding and perforation.

Table 4. The Relative Risks (RRs) of Noncardia Gastric Cancer Among Operated Ulcer Patients, Relative to Unoperated Ones With the Same Ulcer Type

	Noncardia Cancer		
	No. of Cases	Internal Comparison RR (95% CI)*	External Comparison SIR (95% CI)
Duodenal ulcer partial resection			
Not operated	94	Reference	0.5 (0.4–0.7)
Operated overall	23	1.6 (1.0–2.5)	0.8 (0.5–1.2)
Year 2–10 of follow-up	8	1.3 (0.6–2.7)	0.6 (0.3–1.2)
Year 11+ of follow-up	15	1.7 (1.0–3.0)	1.0 (0.6–1.6)
Vagotomy			
Not operated	94	Reference	0.5 (0.4–0.7)
Operated overall	21	1.3 (0.8–2.1)	0.8 (0.5–1.3)
Year 2–10 of follow-up	14	2.0 (1.1–3.7)	1.2 (0.7–2.1)
Year 11+ of follow-up	7	0.8 (0.4–1.7)	0.5 (0.2–1.1)
Gastric ulcer partial resection			
Not operated	462	Reference	2.1 (2.0–2.4)
Operated overall	53	0.6 (0.5–0.8)	1.2 (0.9–1.6)
Year 2–10 of follow-up	27	0.6 (0.4–0.9)	1.0 (0.7–1.5)
Year 11+ of follow-up	26	0.7 (0.5–1.0)	1.5 (1.0–2.1)

These internal comparisons were made with Cox proportional hazard modeling, adjusted for attained age- and sex-. As a measure of RR in the respective subcategories relative to the age-, sex-, and calendar period-matched general population (external comparison), SIR values are given in the rightmost column. The first year of follow-up is excluded in all analyses.
*Relative risk and 95% confidence interval.

vagotomized patients, Table 4), but the risk deficit was less than among unoperated DU patients and statistically nonsignificant. When operated DU patients were directly compared with unoperated ones, a statistically significant 60% risk elevation was unveiled among those who had undergone gastric resection and there was a tendency toward increasing risk with longer follow-up. A statistically nonsignificant 30% increase in risk of noncardia cancers was noted also among those who had been subjected to vagotomy, but it appeared as if the excess was confined to the first 10 yr after the operation.

As opposed to unoperated GU patients, whose risk of noncardia gastric cancer was more than twofold higher than in the matching general population, GU patients with a history of gastric resection had a SIR only slightly above unity (Table 4). In a direct comparison between operated and unoperated GU patients, the former had a statistically significant 40% risk reduction relative to the latter. This risk reduction was slightly smaller when more than 10 yr had elapsed after the operation, and with the matching general population as reference, the SIR rose to 1.5 and became again statistically significant.

DISCUSSION

This large register-based retrospective cohort study with essentially complete and unbiased long-term follow-up persuasively confirms the divergence between duodenal and gastric ulcer in their relationships with gastric cancer (5); with a considerably longer maximum follow-up time, there were no indications that the enigmatic low risk of gastric cancer among DU patients will ultimately return to the same level as in the age-, sex-, and calendar period-matched general population. Nor were there any clear signs that the doubled risk among GU patients will eventually wear off. The present analysis revealed that the low risk among DU patients pertained only to noncardia gastric cancer and not to cardia cancer. The risk elevation among GU patients, on the other hand, was seen for both cancer sites. Another new addition to current knowledge is that partial resection in DU patients, despite the obvious reduction in tissue at risk, was associated with a significant increase in risk of noncardia gastric cancer if these patients were compared with unoperated patients with DU. Because the baseline risk among the latter is so low, operated patients still had a risk that was lower than that in the general population. Gastric resection in GU patients, on the other hand, was linked to significant risk reductions relative to unoperated patients; in comparison with the general population, their risk of noncardia gastric cancer was brought down to normal—at least within the first 10 yr after the operation. Further, vagotomized DU patients had a greater risk of noncardia gastric cancer in the first decade after the operation when compared with unoperated patients with the same disease, but this excess disappeared when 10 yr had elapsed.

The reduction in risk for gastric cancer among DU patients—despite the strong links between DU and *H. pylori*

infection and between *H. pylori* and gastric cancer—is already well established (5, 9, 23) and the mechanisms will not be further discussed herein. It is noteworthy, though, that the apparent protection conferred by DU-related factors seemed not to affect the cardia region. This finding, however, is at odds with two previous studies (23, 24), which reported an inverse relationship also with cardia cancer. These studies, one a case–control analysis within a register of patients at hospitals of the US Department of Veterans Affairs (23), the other a hospital-based case–control study from Taiwan with self-reported ulcer histories (24), both used mixed hospital populations as reference, and left truncation and/or unregistered ulcer diagnoses may have affected the American results. What was classified as cardia cancer may also have differed between the countries. If it is assumed that the DU-related "protection" against gastric cancer is in some way dependent on the interaction between *H. pylori* and the host, then our finding appears more plausible since the relationship between *H. pylori* infection and cardia cancer seems to be weak or nonexisting (25). This issue, however, must still be considered unresolved.

The positive association between GU and cardia cancer risk was more in line with the previous studies; the Taiwanese study found a twofold, albeit statistically nonsignificant, risk elevation (24), while the American VA study saw no association (23). Whereas the mechanisms by which DU might confer protection against cardia cancer remain obscure, a positive association between GU and this cancer may be expected given the hypothesized special importance of N-nitroso compounds in the etiology of cardia cancer (26) and the documented increase in nitrite and N-nitrosamine levels in the stomachs of patients with GU and/or hypochlorhydria (27, 28).

Numerous studies in the past have addressed gastric cancer risk among patients who have undergone partial gastric resection for peptic ulcer, but the results have not been all consistent (29, 30). In fact, the results range from a more than twofold greater to an 80% lower risk (29). More recently, it was realized that both underlying disease and time since operation are important, and that the risk among DU patients is below expectation for some 20 yr, ostensibly due to the reduction of tissue at risk, until it starts to rise (29). To our knowledge, no previous study has compared operated with unoperated patients with the same type of ulcer disease and followed them for prolonged periods. Somewhat surprisingly, surgically resected DU patients had a greater risk, which in stratified analyses was never below that observed among the unoperated ones (although only 30% higher and statistically nonsignificant in the first decade), despite the removal of a substantial part of the organ. However, the risk was never higher than that in the matching general population. This was contrary to the findings among resected GU patients, whose risk was below that among unoperated GU patients for the entire observation period. Because of the high baseline risk among patients with unoperated GU, the risk among operated GU patients never fell below that in the matching general population. With the exception of the close to normal risk relative to the general population among operated GU patients, our findings are consistent with current views in the stump cancer literature but they also shed light on the reasons for the discrepancies between the earlier reports. The reason why resection in GU disease seemingly—and at least temporarily—reduces gastric cancer risk, while the same resection rather seems to already increase the risk within the first decade in DU patients, is unclear. One could speculate that premalignant foci are already common in GU patients so that removal of tissue will have an almost immediate effect. It is even conceivable that a non-negligible number of misdiagnosed malignant gastric ulcers remain silent for several years and thus contribute substantially to the greater gastric cancer incidence among unoperated GU patients. As no malignant or premalignant foci are expected to be present among DU patients who undergo resection, removal of tissue may not have any noticeable effect in the first decades. Why the risk among resected DU patients is slightly higher than among the unoperated still begs an answer. Clearly, chance could be one explanation for our findings. The possibility of confounding by indication must also be entertained, particularly as the excess risk was already noticeable in the first decade after the operation. Operated patients, no doubt, have, on average, more severe disease than the unoperated, but if it is accepted that DU protects against noncardia gastric cancer, it seems counterintuitive to assume that those with more severe disease should have a higher cancer risk. Factors contributing to complications—in turn prompting the decision to operate—should be considered; NSAID use is such a factor, but since it is protective (31), the effect of this confounding is expected to be an even lower risk among operated patients. Smoking may also be such factor, and it is clearly a risk factor for gastric cancer (32). We had no information about smoking habits among our patients, so it is unclear if smokers are enriched among those who undergo surgery. If confounding would be the sole explanation for the difference in risk between operated and unoperated patients, the reason for the differential effects in DU and GU would still need to be explained.

We found a significantly greater risk for noncardia gastric cancer among DU patients who underwent vagotomy, compared with unoperated DU patients, but only during the first 10 yr after the operation. Greater risks have been reported previously (11, 33, 34), and in a previous analysis of parts of the present cohort, followed up until 1988, we found a statistically nonsignificant SIR of 1.3. Although it is tempting to hypothesize that the change in gastric acidity might be conducive to intragastric N-nitrosation and subsequent gastric cancer development, it would probably take many years before a clinically evident cancer would be diagnosed, and one would expect that the risk would increase gradually with follow-up time well beyond the first decade. Therefore, confounding by factors related to the indication for surgery, for instance smoking, must be considered to be the most likely explanation for our finding.

Strengths of this study include the cohort design, the large sample size, and the essentially complete follow-up with incidence as outcome. We also restricted the analysis to "clean" cases of duodenal and gastric ulcer; all patients who had both types of ulcer or who at any point in time switched between the categories were not included. As we had reasonably valid information about both diagnosis and procedure—in validation studies conducted in the Swedish Inpatient Register in 1986 and 1990 errors (stringent criteria) in the diagnostic data were suspected in 17.3 and 14.2% of the records, while erroneous or missing procedure codes were noted in 9.6%, almost half of which were for minor semi-invasive or auxiliary procedures combined with correctly recorded main procedures (35)—it was possible to compare operated patients with unoperated patients and thus to study the effect of surgery independent of the effects of the underlying disease. The restriction to in-hospital patients could be seen as a strength since in-hospital care will likely ensure a somewhat more rigorous disease classification compared with outpatient care. The validity of the outcome data was excellent; the completeness of the Swedish Cancer Register vis-à-vis gastric cancer is 98% and the false-positive rate is 4% (36). However, the coding of site within the stomach is less trustworthy; the completeness of cardia cancer registration was only 69% and the positive predictive value for cardia cancer was 82% in a relatively recent validation study (36). Other caveats worth highlighting include the fact that hospitalized ulcer patients only represent a selected part of the entire pool of ulcer disease in the population; such patients are likely to be sicker, have more complications, have more comorbidity, and to generally have a less healthy lifestyle, compared with patients seen on an outpatient basis. Therefore, generalizations of the reported effect sizes must be done with caution. More importantly, we did not have information about a number of possible confounding factors such as smoking, diet, and drug use, as discussed above. Nor did we have information about possible special indications for surgery such as failure to comply with pharmacological treatment, intractable pain, nutritional problems, and/or weight loss. Another limitation lies in the fact that there was left truncation before the start of the inpatient registration. Some of our unoperated patients who entered the cohort in the early part of the study period could well have been operated on before they came into view in the register. Such misclassification will tend to attenuate differences between operated and unoperated patients. Lastly, since peptic ulcer has been fairly common in the general population, SIRs may have been generally somewhat biased toward the null. As *H. pylori* eradication became first-line treatment for peptic ulcer in the mid 1990s, we employed stratified analyses by follow-up time (before *vs* after year 1990) to explore if the risks diverged, but we did not find any significant difference, suggesting that eradication therapy has not importantly affected the observed associations.

In conclusion, while GU patients have a greater risk for both cardia and noncardia gastric cancer, DU patients have a reduced risk only for noncardia cancer. Although the mechanisms behind the differential relationships between duodenal ulcer disease and gastric cancer of the cardia and noncardia location remains unknown, an analogous differential association between *H. pylori* infection and these two types of cancer suggests that the underlying *H. pylori* infection might also play a pivotal role for the protection. Partial gastric resection seems to add to the risk among DU patients but to reduce risk among those with GU, at least in the first 10–20 yr. While this may suggest that removal of the distal stomach also removes the cause for the differential association of duodenal and gastric ulcer disease, respectively, with gastric cancer risk, confounding by smoking may have contributed to the risk elevation among operated DU patients. Why similar confounding does not seem to have affected the risk among operated GU patients remains an unresolved enigma.

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STUDY HIGHLIGHTS

What Is Current Knowledge

- The differential association of gastric and duodenal ulcer with gastric cancer risk is established.

What Is New Here

- Duodenal ulcer only protects against noncardia cancer. Gastric resection tends to annul the differences between gastric and duodenal ulcer disease in their relationships with gastric cancer risk.

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CONFLICT OF INTEREST

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