

ESOPHAGEAL CANCER

Risk of oesophageal cancer by histology among patients hospitalised for gastroduodenal ulcers

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Oesophageal cancer ranks as the tenth most common cancer in the world.¹ Several epidemiological studies have provided evidence of a dramatic increase in the incidence of oesophageal adenocarcinoma (OAC) in Western countries,^{2–6} whereas a slight decrease has been noted for oesophageal squamous cell carcinoma (OSCC) in some reports^{2–3} although not in all.^{4–5} Additionally, the rates of these two histological types of oesophageal cancer show marked geographical variations.¹

There is strong epidemiological evidence that *Helicobacter pylori* infection, especially with strains carrying the cytotoxin-associated gene A (*CagA*), is associated with a reduced risk of OAC.^{7–12, 13} In fact, based on an intriguing secular concurrence of the rise in oesophageal adenocarcinoma incidence and an obvious decrease in *H pylori* infection prevalence (and a decrease in diseases related to *H pylori* such as duodenal ulcer and gastric ulcer), it has been proposed that these two trends are causally related.¹⁴ On the other hand, a past history of infection with *CagA+* *H pylori* was associated with a more than twofold increased risk of OSCC in our Swedish population-based case-control study.¹⁰

The mechanism by which infection with *H pylori* infection might be reducing the risk of oesophageal adenocarcinoma remains obscure. Some studies suggest that *H pylori* infection, by its ability to induce gastric atrophy and hypochlorhydria, may confer protection against severe reflux, a strong risk factor for oesophageal adenocarcinoma.^{15–16} The inverse association between *H pylori* infection and risk of OAC, however, was seemingly independent of presence or absence of significant gastric atrophy,¹⁰ and pernicious anaemia—accompanied by severe corpus atrophy—is not linked to a reduced OAC risk.¹⁷ Moreover, some reports showed improvement of reflux oesophagitis after eradication of *H pylori* in patients with

Objective: The mechanism behind the epidemiologically evident inverse relation between *Helicobacter pylori* seropositivity and risk of oesophageal adenocarcinoma (OAC) remains obscure. Severe corpus gastritis is unlikely to be in the causal pathway. With the hypothesis of a uniformly low risk, the associations of OAC with duodenal ulcer and gastric ulcer were explored, both linked to *H pylori* infection but with different patterns of bacterial colonisation and intragastric acidity. Possible associations of oesophageal squamous cell carcinoma (OSCC) with these ulcer types were also addressed.

Design and patients: Retrospective cohorts of 61 548 and 81 379 unoperated patients with duodenal ulcer and gastric ulcer, respectively, recorded in the Swedish Inpatient Register since 1965, were followed from the first hospitalisation until the date of any cancer, death, emigration, definitive surgery, or 31 December 2003. Standardised incidence ratios (SIRs), with 95% CIs, expressed relative risk of oesophageal cancer, compared with the Swedish population matched for age, sex and calendar period.

Results: Contrary to expectation, patients with duodenal ulcer had a significant 70% excess risk of OAC (SIR 1.7, 95% CI 1.1 to 2.5). Gastric ulcer was unrelated to OAC (SIR 1.1, 95% CI 0.6 to 1.7). Although duodenal ulcer was non-significantly associated with a small excess of OSCC (SIR 1.3, 95% CI 0.96 to 1.8), gastric ulcer was linked to 80% increased risk (SIR 1.8, 95% CI 1.4 to 2.3).

Conclusion: The inverse association between *H pylori* and OAC does not pertain to all infections. The pattern of gastric colonisation and/or impact on acidity may be important. With the reservation for the possibility of confounding, this study also provides some support for the importance of intragastric environment in the aetiology of OSCC.

duodenal ulcer.^{18–19} *H pylori* designated as a class I gastric carcinogen by International Agency for Research on Cancer (IARC),²⁰ has a central role in peptic ulcer disease aetiology.^{21–22} Ninety per cent of patients with duodenal ulcer and 70–90% of those with gastric ulcer harbour *H pylori* in their stomachs.²³ Duodenal ulcer is associated with antral colonisation and hyperchlorhydria, whereas gastric ulcer is linked to infection of the gastric corpus resulting in a tendency towards hypochlorhydria.

Few studies have explored the risk of oesophageal cancer by histology in patients with peptic ulcer. Duodenal ulcer and gastric ulcer could be seen as two informative models of *H pylori* infection with important differences in site of infection and consequences for gastric acid secretion.

We thus conducted a large retrospective cohort study to investigate the risk of oesophageal cancer by histology among patients hospitalised for gastric ulcer or duodenal ulcer from 1965 to 2003 in Sweden.

MATERIAL AND METHODS

The study population

Data on individual hospitalisations have been collected in the Swedish Inpatient Register by the National Board of Health and Welfare since 1964. Each record contains the National Registration Number (NRN)—an individually unique personal identifier assigned to every Swedish resident from birth or immigration—as well as medical data, including diagnoses at discharge (coded according to the *International Classification of*

Abbreviations: *CagA*, cytotoxin-associated gene A; CI, confidence interval; *H pylori*, *Helicobacter pylori*; NRN, national registration number; OAC, oesophageal adenocarcinoma; OSCC, oesophageal squamous cell carcinoma; SIR, standardised incidence ratio

Diseases, 7th revision (ICD-7)²⁴ to 1968, 8th revision (ICD-8) from 1969 to 1986, 9th revision from 1987 to 1996 and 10th revision thereafter) and surgical procedures (coded according to the Swedish Classification of Operations and Major Procedures to 1996 and the Nordic Medico-Statistical Committee classification of surgical procedures thereafter).

The cohort(s)

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

The NRNs were first checked in the nationwide registers of total population, emigration and causes of death. NRNs that could not be located in any of these registers were regarded as invalid, and for this reason 4731 corresponding records were excluded. We further excluded 22 946 patients with a diagnosis of any cancer before or at time of the index episode, 12 323 individuals who died during the index hospitalisation and 1912 records because of other inconsistencies. Finally, our cohorts encompassed 181 053 individuals.

Follow-up

We linked the NRNs to the nationwide and essentially complete registers of migration and causes of death to obtain censoring information. The national Swedish Cancer Register, established in 1958 and more than 98% complete,²⁵ was used to identify incident cancer cases in the cohort. We only considered first cancers and excluded all benign tumours and cancers found incidentally at autopsy. The Cancer Register used ICD-7 as the coding scheme through the entire study period, and a World Health Organization pathology code was used to record histological types of cancer where applicable. We used ICD-7 code 150 for oesophageal cancer, whereas the pathology code 146 and 096 denoted OSCC and OAC, respectively. The patients in the cohort were followed from the date of discharge from their first recorded in-hospital episode with duodenal ulcer or gastric ulcer until the date of a diagnosis of any cancer, emigration, death, partial/total gastrectomy, vagotomy, or until 31 December 2003, whichever occurred first.

Selection bias may result if prodromal symptoms from yet undetected preclinical oesophageal cancers increase the probability of being hospitalised with a peptic ulcer diagnosis. Therefore, we excluded the first year of follow-up from our analysis to eliminate such selection bias. On the other hand, because most hospitalised patients with peptic ulcer will undergo an upper endoscopy, it is expected that the population is newly screened at time of entry, and that the incidence of oesophageal cancer will be artificially decreased during the first years of follow-up.

Statistical analysis

The standardised incidence ratio (SIR)—the ratio of the observed to the expected number of cancers—was used as a measure of relative risk of oesophageal cancer among patients with duodenal and gastric ulcer. The expected number of cancers was calculated on the basis of the person–time experienced by the cohorts, divided into strata of sex, age (in five-year groups) and calendar year of observation (in five-year intervals). The stratum-specific numbers of accumulated person–years were multiplied by the cancer incidence rates in the corresponding strata, observed in the entire Swedish

population. These incidence rates were computed by using the number of midyear population without a previously reported cancer as the denominator. The 95% CIs for the SIRs were calculated assuming that the observed events followed a Poisson distribution.²⁶ We performed stratified analyses by follow-up duration, sex, presence of complications (bleeding or perforation) at index of hospitalisation, calendar period of index hospitalisation (before versus after 1980), age at entry (less than 50, 50–69, 70–) and the calendar period of follow-up (before versus after 1995). Comparisons of relative risks among strata were done with Poisson regression.

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

RESULTS

The final cohort included 61 548 unoperated patients with duodenal ulcers (64.5% male) and 81 379 unoperated patients with gastric ulcers (52.6% male). Table 1 presents characteristics of patients in the cohorts. The reason for hospitalisation was bleeding for 49% and perforation for 9% of the patients with duodenal ulcer, whereas the corresponding percentages were 47% and 9% for those with gastric ulcer.

Duodenal ulcer

Among the 61 548 unoperated patients with duodenal ulcer followed for an average of 9.1 years, OAC occurred in 27 patients after the first year of follow-up (SIR 1.7; 95% CI 1.1 to 2.5; table 2). Upon stratification, the SIR tended to be slightly higher, and statistically significant, only during years 2–10 of follow-up, but the point estimate, although based on small numbers, remained above unity also after more than 10 years. The relative risk tended to be higher among patients without ulcer complications (SIR 2.6; 95% CI 1.5 to 4.3) compared with those with complicated disease. Trends with sex, age or calendar year at entry could not be interpreted because of small numbers. We found a borderline significant 30% excess risk of OSCC compared with the matching general Swedish population ($n = 44$, SIR 1.3, 95% CI 0.96 to 1.8). The excess was seemingly confined to follow-up years 2–10 and falling with increasing age at index hospitalisation; however, wide CIs precluded firm conclusions.

Gastric ulcer

During follow-up for an average of 7.2 years among 81 379 unoperated patients with gastric ulcer, 18 cases of OAC were diagnosed from year two and onwards (SIR 1.1, 95% CI 0.6 to 1.7; table 3). No conspicuous variation was observed in stratified analyses by follow-up duration, sex, complication history, calendar year and age at entry, but the observed number of cases in each stratum was small and the CIs were wide. In contrast, we observed a significant 80% increase in the relative risk of OSCC ($n = 70$, SIR 1.8, 95% CI 1.4 to 2.3) compared with the age, sex and calendar-period-matched general population. The excess was slightly more marked among men than women, and among younger than older patients, with a significant age-wise trend ($p < 0.01$; table 3).

DISCUSSION

This study was prompted by recent and relatively consistent reports of a strong inverse association between *H pylori* seropositivity and risk of OAC.^{8–10 13} The mechanisms underlying this apparent but enigmatic protection against OAC were first assumed to be *H pylori*-induced atrophic gastritis, hypochlorhydria and reduction of acid reflux into the oesophagus, a

Table 1 Characteristics of patients hospitalised for peptic ulcer in Sweden, 1965–2003

| Characteristics | Duodenal ulcer | Gastric ulcer |
|---|----------------|---------------|
| Number of patients | 61,548 | 81,379 |
| Male (%) | 64.5 | 52.6 |
| Age at index hospitalisation (%), years | | |
| <40 | 12.1 | 6.2 |
| 40–49 | 11.9 | 8.5 |
| 50–59 | 16.2 | 14.3 |
| 60–69 | 19.8 | 20.4 |
| 70–79 | 24.0 | 28.9 |
| ≥80 | 16.0 | 21.7 |
| Mean | 62.1 | 66.7 |
| Reason for index hospitalisation (%) | | |
| Bleeding | 49 | 47 |
| Perforation | 9 | 9 |
| Other | 42 | 44 |
| Total person-years of follow-up* | 524 960 | 576 458 |
| Average follow-up time, years | 9.1 | 7.2 |
| Mean age at diagnosis of cancer,* years | | |
| Oesophageal adenocarcinoma | 72.0 | 75.0 |
| Oesophageal squamous cell carcinoma | 69.0 | 70.0 |

*First year of follow-up was excluded.

strong risk factor for OAC. A closer look at the association, however, revealed that indices of gastric atrophy, either in the form of low pepsinogen I levels¹⁰ or clinical pernicious anaemia¹⁷ were unrelated to risk of OAC. This information suggests that the presumed reduction of acid exposure in the oesophagus may not be critical to the *H pylori*-associated protection against OAC. Because duodenal ulcer could serve as a marker of antrum-predominant *H pylori* infection with hyperchlorhydria, and gastric ulcer could likewise be seen as a marker of *H pylori* infection, but with a more proximal distribution and a tendency rather towards atrophy and hypochlorhydria, the relation of these two types of ulcer to the risk of OAC and OSCC could potentially be informative. We hypothesised that patients with duodenal ulcer, who are almost invariably infected with *H pylori*, would have a low risk of OAC,

and that patients with gastric ulcer would have a similarly reduced risk. Contrary to our expectation, however, the present study revealed a 70% excess risk for OAC among patients with duodenal ulcer, whereas the relative risk among patients with gastric ulcer was close to unity. Because previous studies suggested that isolated CagA seropositivity (a possible marker of a previous burned-out infection²⁷) as well as clinical or serological indicators of atrophic gastritis may be risk factors for OSCC,^{10, 17} we further hypothesised that patients with gastric ulcer, but not those with duodenal ulcer, might have an increased risk for OSCC. The latter hypothesis was essentially confirmed.

Strengths of our study include the large sample size and the cohort design with almost complete follow-up. However, like in most register-based studies, the lack of information about

Table 2 Standardised incidence ratios (SIRs) and their 95% CIs for oesophageal cancer by histology among non-operated patients with duodenal ulcer, by follow-up duration, sex, presence of complications and calendar year of index hospitalisation*

| | Adenocarcinoma | | Squamous cell carcinoma | |
|--|-----------------|---------------|-------------------------|----------------|
| | Number of cases | SIR (95% CI) | Number of cases | SIR (95% CI) |
| Overall | 27 | 1.7 (1.1–2.5) | 44 | 1.3 (0.96–1.8) |
| Follow-up duration, years | | | | |
| 2–10 | 17 | 1.9 (1.1–3.1) | 33 | 1.6 (1.1–2.2) |
| 11+ | 10 | 1.5 (0.7–2.8) | 11 | 0.9 (0.5–1.6) |
| p for trend | | 0.15 | | 0.01 |
| Sex | | | | |
| Men | 23 | 1.7 (1.1–2.5) | 34 | 1.3 (0.9–1.8) |
| Women | 4 | 2.1 (0.6–5.5) | 10 | 1.5 (0.7–2.7) |
| Complication† | | | | |
| Yes | 12 | 1.2 (0.6–2.1) | 30 | 1.4 (0.95–2.0) |
| No | 15 | 2.6 (1.5–4.3) | 14 | 1.2 (0.6–2.0) |
| Calendar year of index hospitalisation | | | | |
| 1965–79 | 10 | 2.1 (1.0–3.8) | 18 | 1.3 (0.8–2.1) |
| 1980–2003 | 17 | 1.6 (0.9–2.5) | 26 | 1.3 (0.9–2.0) |
| Age at entry | | | | |
| <50 | 6 | 2.4 (0.9–5.1) | 9 | 2.0 (0.9–3.8) |
| 50–69 | 15 | 1.9 (1.1–3.1) | 25 | 1.4 (0.9–2.1) |
| 70– | 6 | 1.2 (0.4–2.5) | 10 | 0.9 (0.4–1.6) |
| p for trend | | 0.09 | | <0.001 |
| Calendar year of follow-up | | | | |
| 1965–94 | 13 | 2.3 (1.2–4.0) | 25 | 1.2 (0.8–1.8) |
| 1995–2003 | 14 | 1.4 (0.8–2.3) | 19 | 1.5 (0.9–2.3) |

*First year of follow-up was excluded.

†Including bleeding and perforation.

Table 3 Standardised incidence ratios (SIRs) and their 95% CIs for oesophageal cancer by histology among unoperated patients with gastric ulcer, by follow-up duration, sex, presence of complications and calendar year of index hospitalisation*

| | Adenocarcinoma | | Squamous cell carcinoma | |
|--|-----------------|---------------|-------------------------|---------------|
| | Number of cases | SIR (95% CI) | Number of cases | SIR (95% CI) |
| Overall | 18 | 1.1 (0.6–1.7) | 70 | 1.8 (1.4–2.3) |
| Follow-up duration, years | | | | |
| 2–10 | 12 | 1.1 (0.6–2.0) | 48 | 1.8 (1.3–2.4) |
| 11+ | 6 | 1.0 (0.4–2.2) | 22 | 1.9 (1.2–2.9) |
| Sex | | | | |
| Men | 15 | 1.1 (0.6–1.9) | 53 | 2.0 (1.5–2.6) |
| Women | 3 | 0.9 (0.2–2.7) | 17 | 1.5 (0.8–2.3) |
| Complication† | | | | |
| Yes | 11 | 1.1 (0.6–2.0) | 39 | 1.7 (1.2–2.3) |
| No | 7 | 1.1 (0.4–2.2) | 31 | 2.1 (1.4–2.9) |
| Calendar year of index hospitalisation | | | | |
| 1965–79 | 4 | 1.0 (0.3–2.4) | 26 | 1.9 (1.2–2.8) |
| 1980–2003 | 14 | 1.1 (0.6–1.9) | 44 | 1.8 (1.3–2.4) |
| Age at entry | | | | |
| <50 | 2 | 1.2 (0.1–4.2) | 10 | 3.2 (1.5–5.8) |
| 50–69 | 10 | 1.2 (0.6–2.3) | 43 | 2.2 (1.6–3.0) |
| 70– | 6 | 0.9 (0.3–1.9) | 17 | 1.1 (0.6–1.7) |
| P for trend | | 0.49 | | <0.01 |
| Calendar year of follow-up | | | | |
| 1965–94 | 5 | 0.8 (0.3–1.9) | 38 | 1.6 (1.1–2.2) |
| 1995–2003 | 13 | 1.3 (0.7–2.1) | 32 | 2.2 (1.5–3.1) |

*First year of follow-up was excluded

†Including bleeding and perforation.

possible confounding factors is an important limitation. Smoking—linked to both duodenal ulcer and OAC—is such a factor that could have attenuated an *H pylori*-driven inverse association between these two diseases. However, the strength of the associations of smoking with both duodenal ulcer and OAC is comparably moderate and is unlikely to have shifted a 70–80% protection, as judged from the direct studies on *H pylori* seroprevalence and OAC risk,^{8–10, 13} to a 70% increased risk. The comparably weak link between smoking and unoperated duodenal ulcer in our cohort is demonstrated by the moderate association (SIR 1.6) with lung cancer risk (data not shown). Cyclooxygenase inhibitors such as aspirin or some other non-steroidal anti-inflammatory drugs constitute other factors, which are tentatively associated with both peptic ulcer and OAC,^{28, 29} and could thus be true confounders. However, because these drugs seem to protect against OAC, such confounding would tend to strengthen a true inverse association, not to cancel it.

Until *H pylori* eradication became first-line treatment for peptic ulcer in the mid-1990s, H₂-receptor antagonists and proton pump inhibitors were widely and generously used in these patients, particularly in those with duodenal ulcer. Although we lack information about medications in our register data, it seems reasonable to assume that aggressive treatment, including long-term maintenance therapy, was common in our cohorts, consisting of in-hospital patients with a high prevalence of complications. It is yet to be established if acid inhibition protects against OAC, but because of the apparent key role of gastro-oesophageal reflux in OAC aetiology, such treatment is more likely to reduce the risk than to increase it. Therefore, it is inconceivable that the widespread use of H₂-receptor antagonists or proton pump inhibitors would explain the increased OAC risk among duodenal ulcer patients. If anything, such treatment might have led to some underestimation of the duodenal ulcer-related excess of OAC.

A second limitation is the lack of information about factual *H pylori* status. Although this weakness may seem less important among our almost invariably infected duodenal

ulcer patients, a non-negligible proportion of our unexposed comparison group—the age, sex and calendar period-matched general Swedish population—carried antibodies to *H pylori*. Hence, whereas studies with individual data on *H pylori* status compare exposed groups, in which almost 100% are truly infected, with unexposed groups containing close to 0% infected, the corresponding percentages in our study are likely to be 90% versus 50–70%. This will attenuate any measure of association, but it will not reverse them.

In the analysis of gastric ulcer, the combination of confounding by smoking and attenuation due to “misclassification” of the *H pylori* status among the supposedly exposed ulcer patients (but only approximately 80% were infected) and the purportedly unexposed comparison population (but with a mean age of 66.7 years at entry probably close to 70% were infected) could conceivably have removed a substantial underlying inverse association between *H pylori* and OAC. Therefore, the absence of association should not be overinterpreted. A similar caveat must be highlighted for the moderately strong positive association between gastric ulcer and OSCC, which could potentially be explained by confounding by smoking, a strong risk factor for OSCC. The differential associations for gastric ulcer and duodenal ulcer, however, somewhat disagree with such confounding as the sole explanation.

Although recent research¹⁰ has challenged the old hypothesis that *H pylori* protects against OAC by atrophic gastritis and hypoacidity, it appears that our present findings among patients with duodenal and gastric ulcers are, again, more in line with the original explanation. The oesophageal mucosa in individuals with duodenal ulcer is, on average, more exposed to gastric acid than that in healthy individuals,³⁰ whereas it is likely to be less exposed in patients with gastric ulcer, linked to corpus gastritis and hypoacidity. According to the old hypoacidity hypothesis, gastric ulcer patients, and those with manifest atrophic gastritis, should be the ones most protected against OAC. As discussed above, the *H pylori*-associated protection may not be faithfully reflected in the comparison with the general population, and what remains of the effect

might have been cancelled by confounding from smoking. An alternative but admittedly speculative explanation is that the non-surgical treatment offered to these patients in some way modifies the inverse *H pylori*-OAC relation.

With due reservations, our finding of a positive association between gastric ulcer and risk of OSCC adds some further support for the hypothesis that the intragastric environment fostered by corpus atrophy may play a role in OSCC aetiology.¹⁰⁻³¹ In the atrophic, hypoacidic stomach, microorganisms other than *H pylori* may thrive and generate intragastric nitrosamines.³² N-nitrosamines are suspected as a key risk factor for OSCC.³³ Such tumours can be induced by N-nitroso compounds in animal models³⁴⁻³⁶ and endogenous nitrosamines that can reach the oesophageal mucosa through one or more unknown ways (reflux or through submucosal veins) seem to play a central role.³⁷

In conclusion, this study suggests that the repeatedly confirmed strong inverse relation between *H pylori* seropositivity and risk of OAC does not pertain to all infections. It appears as if the pattern of gastric colonisation and/or the clinical consequences in the stomach plays an important role.

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