STOMACH

Antibiotic treatment and risk of gastric cancer

K Fall, W Ye, O Nyrén

Gut 2006;**55**:793–796. doi: 10.1136/gut.2006.091850

See end of article for authors' affiliations

Correspondence to: Dr K Fall, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Box 281, S-171 77 Stockholm, Sweden; Katja.Fall@ki.se

Revised version received 16 January 2006
Accepted for publication 15 February 2006

Background/aims: *Helicobacter pylori* infection is undoubtedly an important risk factor for gastric cancer. It remains unclear however whether antibiotic treatment may prevent gastric cancer development. Our aim was to assess long term gastric cancer risks in historic cohorts of patients presumed to have been heavily exposed to antibiotics.
Subjects: Using the Swedish Inpatient Register, we identified 501 757 individuals discharged with any one of 10 selected infectious disease diagnoses between 1970 and 2003.
Methods: We counted person time and non-cardia gastric cancer occurrences through linkage to virtually complete population and health care registers. Standardised incidence ratios (SIRs) were calculated for comparisons with cancer incidence rates of the general population in Sweden.
Results: No reduction in gastric cancer risk was observed in the infectious disease cohort in total (SIR 1.08 (95% confidence intervals 1.00–1.17) or for any of the presumed antibiotic regimens. There were no clear trends towards decreasing risk with time of follow up, but the risk tended to fall with increasing age at first hospitalisation for the infection ($p<0.04$).
Conclusions: Our results do not confirm earlier observational findings of a reduced risk of gastric cancer following exposure to heavy antibiotic treatment among hip replacement patients. Suboptimal drug regimens, inadequate timing of *H pylori* eradication, or insufficient follow up time may possibly explain the lack of association in this setting. Although our findings do not rule out the cancer preventive potential of *H pylori* eradication, they emphasise that detection of such an effect, if any, may require considerable efforts.

Helicobacter pylori is undoubtedly an important risk factor for gastric cancer.[1] The benefit of *H pylori* eradication remains to be confirmed however before large scale gastric cancer prevention programmes can be implemented. Randomised eradication trials using gastric cancer as an end point would provide the missing evidence, and the first suggestive results have recently been published.[2] Such studies however require large samples and lengthy follow up times, even in populations with a high gastric cancer incidence. Conclusive results, if at all attainable, are unlikely to be available in the near future.

Using available data from the Swedish Inpatient Register and Cancer Register, we have previously approached the question of whether antibiotic treatment may reduce the risk of gastric cancer. In a cohort of 39 000 individuals who underwent hip replacement surgery, we found a declining risk of gastric cancer with increasing time after surgery,[3] a finding that has been confirmed by others.[4] We hypothesised that the prophylactic antibiotic treatment given at the time of surgery caused incidental eradication of *H pylori* and, a case control study ''nested'' within the original cohort, indicated an inverse association between antibiotic treatment and subsequent development of gastric cancer.[5]

The indicative, but not convincing, evidence of an inverse relationship between antibiotic treatment and gastric cancer risk in humans requires further confirmation. In the present study, we aimed to assess the risk of gastric cancer in a large cohort of patients who were hospitalised for any one of 10 selected infectious diseases associated with a broad range of antibiotic regimens.

METHODS

Using the Swedish Inpatient Register, we identified 501 757 individuals who had been discharged from inpatient care with a diagnosis of pyelonephritis, chronic cystitis, endocarditis, chronic rheumatic heart disease, pelvic infection, rheumatic fever, tonsillitis, venereal infection, osteomyelitis, or meningitis between 1970 and 2003. As described previously,[3] we verified the validity of the national registration numbers (NRNs), unique personal identifiers assigned to all Swedish residents, through record linkages to the nationwide and essentially complete registers of Total Population, Death, and Emigration. The latter two registers also provided dates for censoring. Linkage of the NRNs in the cohort to the 98% complete[6] nationwide Swedish Cancer Register identified all prevalent cases of non-cardia gastric cancer at entry and all incident cases during follow up. As a separate code for gastric cancer in the cardia was first introduced into the Swedish Cancer Register in 1969, cases and person years were accumulated from 1970, one year after the coding change, to ensure quality of data. The cohort members were followed from the date of first hospitalisation for the infectious disease diagnosis until first cancer diagnosis, death, emigration, or end of follow up (31 December 2003), whichever occurred first. Recorded comorbidity was used to shed light on possible confounding factors. A history of hospitalisation for rheumatoid arthritis or osteoarthritis was used as an indicator variable for substantial exposure to aspirin or other non-steroidal anti-inflammatory drugs. The incidence of lung cancer in the studied cohort, relative to that in the corresponding background population, served as a marker of smoking habits among the studied subjects.

The standardised incidence ratio (SIR), the ratio of the observed to the expected number of cancers, derived from the age, sex, and calendar period matched Swedish population, estimated relative risk. Confidence intervals of SIRs were calculated assuming that the observed number of cancers followed a Poisson distribution.[7] As subtle symptoms from yet undiagnosed gastric cancer will increase the likelihood of hospitalisation for any disease, we excluded all cancers and

Abbreviations: SIR, standardised incidence ratio; NRN, national registration number

Table 1 Cohort of patients hospitalised for selected infectious diseases in Sweden 1970–2003

	Men	Women	Total
Total No	189 613	312 144	501 757
Mean follow up time (y)	10.0	12.9	11.8
Person years at risk	1 895 058	4 019 167	5 914 225
Mean age at entry (y)	43.3	38.9	40.6
Pyelonephritis	53.6	44.1	47.4
Chronic cystitis	69.4	65.9	67.0
Meningitis	31.5	33.9	32.6
Endocarditis, acute	58.6	63.0	60.4
Endocarditis, chronic	67.3	73.1	70.1
Chronic rheumatic heart disease	63.2	67.4	65.5
Rheumatic fever	44.8	51.5	47.0
Osteomyelitis	46.6	49.8	47.9
Tonsillitis	19.3	21.4	20.4
Venereal disease	38.8	27.3	30.0
Pelvic infection	48.1	28.0	28.0

person years accrued during the first year of follow up in the analyses to avoid selection bias.

RESULTS

Characteristics of the cohort are presented in table 1. In total, the cohort generated 5 914 225 person years of observation. Mean follow up time was 11.8 years and the male:female ratio was 1:2.

After exclusion of the first year of follow up, we identified 645 incident cases of non-cardia gastric cancer compared with 596 expected. This small excess was not statistically significant (SIR 1.08 (95% confidence interval (CI) 1.00–1.17)) (table 2). The modest risk increase was only apparent in women (SIR 1.18 (95% CI 1.06–1.31)) and not in men (SIR 0.99 (95% CI 0.89–1.11)). Patients less than 50 years of age at infectious disease diagnosis had a 25% increased risk of non-cardia gastric cancer compared with the age, sex, and calendar period matched background population. Relative risks tended to fall with increasing age at first hospitalisation for the infection (p for trend = 0.04), and after the age of 70 years the risk appeared to be the same for patients in the antibiotic exposed cohort and in the corresponding background population. There was no association between duration of follow up and non-cardia gastric cancer risk.

Table 2 Standardised incidence ratios (SIRs) and 95% confidence interval (CI) for non-cardia gastric cancer among subjects hospitalised for infectious disease* by selected cohort characteristics

Characteristic	Observed No cancer cases	SIR (95% CI)
All†	645	1.08 (1.00–1.17)
Sex		
Male	310	0.99 (0.89–1.11)
Female	335	1.18 (1.06–1.31)
Age at index hospitalisation (y)		
<50	112	1.25 (1.03–1.50)
50–59	91	1.11 (0.89–1.36)
60–69	179	1.13 (0.97–1.31)
70–79	191	0.99 (0.86–1.14)
80+	72	0.98 (0.77–1.23)
Trend		0.04
Follow up (y)		
1–4	266	1.07 (0.95–1.21)
5–9	153	0.94 (0.79–1.10)
10–14	109	1.23 (1.01–1.49)
15–19	63	1.24 (0.96–1.59)
20+	54	1.18 (0.89–1.54)

*Patients hospitalised with pyelonephritis, chronic cystitis, endocarditis, chronic rheumatic heart disease, pelvic infection, rheumatic fever, tonsillitis, venereal disease, osteomyelitis, or meningitis between 1970 and 2003.
†All person time and all 150 non-cardia gastric cancer cases that had occurred during the first year of follow up were excluded.

Stratification according to type of infectious disease (and thus to probable antibiotic regimen) did not reveal any clear differences over strata (table 3). Furthermore, within these subgroups of presumed treatment, no clear effect of follow up time was apparent (table 4). Neither total number of hospitalisations (data not shown) nor clustered treatments (⩾3 times within a period of 12 months anytime during follow up) affected gastric cancer risk (table 4).

There was, if anything, a slight suggestion that conditions linked with intake of aspirin or other non-steroid anti-inflammatory drugs may be associated with a lower risk of gastric cancer risk (table 5). As an indicator of the possible confounding of smoking, we assessed the risk of lung cancer and observed a statistically significant 25% increased risk in the exposed cohort (SIR 1.25 (95% CI 1.19–1.31)) (data not shown).

DISCUSSION

These data do not support the previous observational finding of a reduced risk of gastric cancer after exposure to heavy antibiotic treatment.[5] We hypothesised that several antibiotic treatments would have the potential to eradicate *H pylori*, preferably in an environment with low acidity, and we assumed that the most effective treatment would be targeted at the Gram negative bacterial spectrum. None of the infectious disease diagnoses was however associated with a clearly reduced risk of gastric cancer. Assuming a latency time of many years between *H pylori* infection and cancer development, any effect of successful eradication would be expected to increase with time. For our data, no such pattern was evident overall, or in any of the studied subcohorts.

The strengths of the present study include its large size, and the unbiased and close to complete follow up. A weakness of most registry based studies is the inability to control for all relevant confounding factors. Low socioeconomic status is a known risk factor for both infectious disease and gastric cancer, the latter association probably mediated via a higher prevalence of *H pylori* infection, and confounding by this factor could mask an inverse association. Smoking is another plausible confounder, as indicated by the increased risk for lung cancer in the studied cohort. Even if such confounding increased the baseline risk, a true protective effect of antibiotic treatment would still be anticipated to result in a downward trend in risk with increasing follow up time. As we had no further information

Table 3 Standardised incidence ratios (SIRs) and 95% confidence interval (CI) for non-cardia gastric cancer among subjects hospitalised for infectious disease, by diagnosis

Treatment directed against/diagnosis	Observed No cancer cases	SIR (95% CI)
Predominantly Gram negative bacteria		
All*	293	1.08 (0.96–1.21)
Chronic cystitis	33	1.01 (0.70–1.42)
Pyelonephritis	261	1.08 (0.95–1.22)
Predominantly Gram positive bacteria		
All*	163	1.09 (0.93–1.27)
Tonsillitis	45	1.04 (0.76–1.39)
Osteomyelitis	12	0.75 (0.39–1.30)
Rheumatic fever	18	1.27 (0.75–2.00)
Rheumatic heart disease	89	1.16 (0.93–1.42)
Mixed Gram positive and negative bacteria		
All*	175	1.03 (0.89–1.20)
Endocarditis, acute	9	0.63 (0.29–1.20)
Endocarditis, chronic	153	1.07 (0.91–1.26)
Bacterial meningitis	15	0.89 (0.50–1.46)
Bacteria with intracellular growth		
All*	61	1.12 (0.85–1.44)
Pelvic infection	36	1.04 (0.73–1.44)
Venereal infection	28	1.32 (0.88–1.91)

*Numbers do not sum to the total as diagnosis categories are not mutually exclusive.

Table 4 Standardised incidence ratios (SIRs) and 95% confidence interval (CI) for non-cardia gastric cancer among subjects hospitalised for infectious disease, by spectrum of antibiotic treatment, follow up time, and frequency of treatment

Treatment directed against	Observed No cancer cases	SIR (95%CI)
Predominantly Gram negative bacteria*		
Follow up time (y)		
1–4	119	1.01 (0.83–1.20)
5–9	75	0.97 (0.77–1.22)
10–14	61	1.51 (1.16–1.94)
15–20	24	1.17 (0.75–1.74)
20+	14	0.96 (0.52–1.61)
p (trend)		0.22
Frequency of treatments		
<3 times/y	267	1.06 (0.94–1.19)
⩾3 times/y	26	1.40 (0.91–2.05)
Predominantly Gram positive bacteria†		
Follow up time (y)		
1–4	63	1.16 (0.89–1.49)
5–9	34	0.83 (0.57–1.15)
10–14	27	1.06 (0.70–1.54
15–20	21	1.53 (0.84–2.07)
20+	18	1.40 (0.83–2.22)
p (trend)		0.35
Frequency of treatments		
< 3 times/year	137	1.09 (0.91–1.30)
⩾3 times/year	33	1.08 (0.74–1.52)
Mixed Gram positive and negative bacteria‡		
Follow up time (y)		
1–4	100	1.14 (0.93–1.39)
5–9	48	0.97 (0.72–1.29)
10–14	12	0.63 (0.32–1.10)
15–20	10	1.36 (0.65–2.49)
20+	3	0.76 (0.16–2.21)
p (trend)		0.22
Frequency of treatments		
<3 times/year	123	1.15 (0.96–1.37)
⩾3 times/year	50	0.83 (0.61–1.09)
Bacteria with intracellular growth§		
Follow up time (y)		
1–4	9	1.05 (0.48–2.00)
5–9	5	0.52 (0.17–1.21)
10–14	13	1.38 (0.76–2.32)
15–20	14	1.28 (0.68–2.18)
20+	20	1.24 (0.76–1.92)
p (trend)		0.27
Frequency of treatments		
<3 times/year	61	1.17 (0.89–1.50)
⩾3 times/year	0	0.0

Categories include *chronic cystitis, pyelonephritis, †tonsillitis, osteomyelitis, rheumatic fever, rheumatic heart disease, ‡endocarditis, bacterial meningitis, §pelvic infection, venereal infection.

Table 5 Standardised incidence ratios (SIRs) and 95% confidence interval (CI) for gastric cancer among subjects hospitalised for infectious disease, by comorbid conditions associated with exposure to aspirin and other non-steroid anti-inflammatory drugs

Comorbidity	Observed No cancer cases	SIR (95%CI)
Rheumatoid arthritis		
No	633	1.09 (1.00–1.17)
Yes	12	0.92 (0.47–1.60)
Osteoarthritis		
No	602	1.10 (1.01–1.19)
Yes	43	0.92 (0.66–1.24)

about the factual use of antibiotics than the infectious disease diagnosis, and the prescription of antibiotics to the general population is high, misclassification of exposure may be considerable. Such misclassification should be non-differential and may thus have diluted the hypothesised protective effect of antibiotic treatment.

There are several possible explanations for the inconsistency between the present and previous finding among hip replacement patients.[3 5] It should be emphasised that the hip replacement study offered some advantages in comparison with the present investigation. Firstly, there is little reason to believe that the underlying hip diseases or indications for replacement surgery in this setting are related to the probability of *H pylori* infection or to other known risk factors for gastric cancer. Therefore, the baseline risk of gastric cancer was expected to be similar to that in the general population. Secondly, as allocation of antibiotic treatment was not individualised, but administered according to standardised local protocols, confounding by indication was unlikely. The possibility of a chance finding however still remains.

Intense exposure to aspirin and other non-steroid anti-inflammatory drugs may, alternatively, have influenced gastric cancer risk among the hip replacement patients, who typically have intractable pain prior to their operations. Regular use of this type of drug has been linked to a reduced risk of gastric cancer.[8–10] Our analyses of comorbidity associated with high exposure to anti-inflammatory drugs tended to, if anything, confirm these findings.

There may be various reasons for the lack of association between antibiotic treatment and gastric cancer risk in our study. Given the possibility of very long induction and latency periods before a gastric neoplasm becomes clinically evident, the follow up may simply have been too short. No more than 54 of the 645 observed gastric cancers occurred 20 or more years after entry into the cohort. Suboptimal antibiotic treatment is another possible reason. Even if some infections, in fact, healed, the eradication rate may not have been sufficiently different from that in the general population, which is also frequently exposed to antibiotic treatment. A third explanation could be that even if *H pylori* eradication was achieved, prevention of gastric cancer may not have been attained because the carcinogenic process had already reached its ''point of no return'' in most patients. However, in the present study, young age at infectious disease diagnosis seemed to be associated with an increased gastric cancer risk, rather than the opposite effect. There are indications, although challenged by the recent findings of Wong and colleagues,[2] that the cancer process can be halted even when precarcinogenic lesions have developed.[11–13] We speculated previously that incidental eradication by normally ineffectual antibiotics may be facilitated in older patients[5] as the prevalence of gastric atrophy—a condition with elevated intragastric pH—increases with age. The observed trend of a falling gastric cancer risk with increasing age at infectious disease diagnosis (and treatment) lends some limited support to these speculations.

In summary, these data failed to confirm previous findings of a reduced risk of gastric cancer following heavy antibiotic treatment. A true protective effect of antibiotic treatment on gastric cancer occurrence may theoretically have been masked by confounding or diluted by exposure misclassification. Furthermore, the follow up time may have been too short. Alternatively, eradication may not have been accomplished because of insufficient doses of antibiotics or inappropriate timing of treatment. Hence these results do not rule out the prospect of preventing gastric cancer by *H pylori* eradication. They are however a reminder of the need for targeted and efficient treatment, large sample size, and probably a very long follow up if a cancer preventive effect is to be detected in a randomised trial. The results of our previously published study, where a dramatic fall in gastric cancer incidence was observed within 5–10 years,[3] may have been an example of confounding by the possibly protective effect of aspirin and other non-steroid anti-inflammatory drugs.

Authors' affiliations

K Fall, W Ye, O Nyrén, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

This work was supported by a grant from the Swedish Cancer Society 3797-B96-01XAA

Conflict of interest: None declared.

REFERENCES

1 **Forman D**. Helicobacter pylori: the gastric cancer problem. *Gut* 1998;**43**(suppl 1):S33–4.
2 **Wong BC**, Lam SK, Wong WM, *et al*. Helicobacter pylori eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. *JAMA* 2004;**291**:187–94.
3 **Nyren O**, McLaughlin JK, Gridley G, *et al*. Cancer risk after hip replacement with metal implants: a population- based cohort study in Sweden. *J Natl Cancer Inst* 1995;**87**:28–33.
4 **Olsen JH**, McLaughlin JK, Nyren O, *et al*. Hip and knee implantations among patients with osteoarthritis and risk of cancer: a record-linkage study from Denmark. *Int J Cancer* 1999;**81**:719–22.
5 **Akre K**, Signorello LB, Engstrand L, *et al*. Risk for gastric cancer after antibiotic prophylaxis in patients undergoing hip replacement. *Cancer Res* 2000;**60**:6376–80.
6 **Mattsson B**, Wallgren A. Completeness of the Swedish Cancer Register. Non-notified cancer cases recorded on death certificates in 1978. *Acta Radiol Oncol* 1984;**23**:305–13.
7 **Bailar J**. Significance factors for the ratio of a Poisson variable to its expectation. *Biometrics* 1964;**20**:639–643.
8 **Farrow DC**, Vaughan TL, Hansten PD, *et al*. Use of aspirin and other nonsteroidal anti-inflammatory drugs and risk of esophageal and gastric cancer. *Cancer Epidemiol Biomarkers Prev* 1998;**7**:97–102.
9 **Zaridze D**, Borisova E, Maximovitch D, *et al*. Aspirin protects against gastric cancer: results of a case-control study from Moscow, Russia. *Int J Cancer* 1999;**82**:473–6.
10 **Akre K**, Ekstrom AM, Signorello LB, *et al*. Aspirin and risk for gastric cancer: a population-based case-control study in Sweden. *Br J Cancer* 2001;**84**:965–8.
11 **Correa P**, Fontham ET, Bravo JC, *et al*. Chemoprevention of gastric dysplasia: randomized trial of antioxidant supplements and anti-helicobacter pylori therapy. *J Natl Cancer Inst* 2000;**92**:1881–8.
12 **Sung JJ**, Lin SR, Ching JY, *et al*. Atrophy and intestinal metaplasia one year after cure of *H. pylori* infection: a prospective, randomized study. *Gastroenterology* 2000;**119**:7–14.
13 **Ley C**, Mohar A, Guarner J, *et al*. *Helicobacter pylori* eradication and gastric preneoplastic conditions: a randomized, double-blind, placebo-controlled trial. *Cancer Epidemiol Biomarkers Prev* 2004;**13**:4–10.