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Risk for Gastric Cancer after Antibiotic Prophylaxis in Patients Undergoing Hip Replacement[1]

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ABSTRACT

Despite strong evidence of an association between *Helicobacter pylori* and gastric cancer, the benefit of eradicating *H. pylori* infection is unknown. Our aim was to test the hypothesis that exposure to high doses of antibiotics reduces risk for gastric cancer via possible eradication of *H. pylori.* We conducted a nationwide case-control study nested in a cohort of 39,154 patients who underwent hip replacement surgery between 1965 and 1983. Such patients frequently receive prophylactic antibiotic treatment. During follow-up through 1989, we identified 189 incident cases of gastric cancer. For each case, three controls were selected from the cohort. Exposure data were abstracted from hospital records. Blood samples from a separate cohort undergoing hip replacement surgery were analyzed for anti-*H. pylori* IgG before and after surgery. Both long-term antibiotic treatment before surgery [odds ratio (OR), 0.3; 95% confidence interval (CI), 0.1–0.7] and prophylactic antibiotic treatment (OR, 0.7; 95% CI, 0.5–1.1) conferred a reduction in gastric cancer risk. The reduction appeared stronger after 5 years (OR, 0.6; 95% CI, 0.3–1.2) than during shorter follow-up after hip replacement (OR, 0.8; 95% CI, 0.4–1.7). There was an apparent decrease in risk with increasing body weight-adjusted doses of antibiotics ($P = 0.13$). However, the rate of *H. pylori* antibody disappearance was not strikingly higher in the cohort of patients undergoing hip replacement than in a control cohort. Our findings provide indirect support for the hypothesis that treatment with antibiotics at a relatively advanced age reduces the risk of gastric cancer.

INTRODUCTION

Strong epidemiological evidence of an association with gastric cancer has resulted in the classification of *Helicobacter pylori* as a human carcinogen (1), but a causal link has not been clearly established. Recently, three experimental studies provided evidence that *H. pylori* infection induces gastric cancer in animals (2–4). However, a demonstrable decrease in gastric cancer incidence in humans after eradication of *H. pylori* would provide the missing evidence of causality and should be required before large-scale prevention programs are implemented. However, clinical eradication trials with cancer incidence as an end point are difficult to perform; they require large samples and lengthy follow-up, even in populations with high gastric cancer incidence.

We saw an opportunity to obtain indirect evidence in support of a causal relationship between *H. pylori* and gastric cancer by evaluating, in an observational study, gastric cancer risk among patients exposed to heavy antibiotic treatment. In a cohort study based on record linkage between the Swedish Inpatient Register and Cancer Register (5), we previously observed a steady decrease in gastric cancer risk with time after hip replacement surgery among both males and females. The risk was 10%, 26%, and 42% lower than that of the background population after 1, 5, and 10 years, respectively. These results were recently confirmed in a similar study from Denmark (6). A possible explanation for the observed reduction in gastric cancer risk is incidental eradication of *H. pylori* by the prophylactic antibiotic treatment given to a majority of the patients. Indeed, incidental eradication of *H. pylori* has previously been observed among heart and liver transplant recipients in association with antibiotic treatment (7, 8).

To test the hypothesis that antibiotic treatment reduces risk for gastric cancer, perhaps with a dose-dependent effect, we abstracted detailed information on antibiotic treatment in a case-control study nested within the original cohort of hip replacement patients (5). To test our proposed chain of evidence linking *H. pylori* causally to gastric cancer, we also used serum samples from another, more recent cohort of patients undergoing hip replacement surgery with prophylactic antibiotic treatment to determine the incidence of anti-*H. pylori* IgG seroreversion.

MATERIALS AND METHODS

For the present study, we have used three independent cohorts (cohorts I, II, and III) that will be described below.

Prophylactic Antibiotics and Gastric Cancer Risk (Cohort I). The Swedish Inpatient Register, established in 1965, keeps records of all instances of somatic in-hospital care in the areas covered by the registration (9). Cohort I, which has been described previously (5), consisted of all patients recorded in this register as having undergone hip replacement surgery (Swedish Classification of Operations and Major Procedures, codes 8410, 8411, 8412, and 8419) between 1965 and 1983. The first such surgery for each cohort member during this time period was designated as the "index" surgery. There were 39,154 patients (14,869 men and 24,285 women). The mean age at entry into the cohort was 67.7 years, and the mean calendar year at entry was 1978. Primary diagnoses at the time of hip replacement surgery were osteoarthritis (64%), late sequelae after fracture (17%), acute fracture (10%), rheumatoid arthritis (5%), and other (5%).

Use of the individually unique national registration number permitted linkage of information across registries. Through linkage to the more than 97% complete National Swedish Cancer Registry (10), established in 1958, we identified all incident cases of gastric cancer (International Classification of Diseases-7, code 151) in the cohort from the start of follow-up (time of index surgery) until censoring due to a cancer diagnosis, death, emigration, or end of follow-up (December 31, 1989), whichever occurred first. Dates of death and emigration were obtained through record linkages to the essentially complete national registers of death and emigration. Mean duration of follow-up for the cohort was 8.4 years, and it generated a total of 327,922 person-years at risk.

Nested Case-Control Study within Cohort I. A total of 189 cases of gastric cancer occurred during follow-up. For each case, three controls who were alive and living in Sweden at the time of cancer diagnosis of the index case were randomly selected from the cohort, matched on age (±5 years) and date of index surgery (±5 years). Only exposures prior to 1 year before cancer diagnosis in the case and the corresponding follow-up time for the control were considered. We were able to retrieve orthopedic medical records for 92% of the cases and 86% of the controls. Due to missing records, 15 incomplete matched

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sets (in which there was no case or no control) had to be excluded. Thus, 174 cases and 462 individually matched controls were eventually included in the study.

From the orthopedic records, data were collected on the index operation and on all other hip replacement procedures carried out during the follow-up period. Information about maximum and cumulative antibiotic doses for prophylactic purposes were abstracted and defined as follows: (*a*) maximum dose was the highest daily dose of prophylactic antibiotics received at any recorded surgical procedure; and (*b*) cumulative dose was calculated by summing the prophylactic antibiotic doses for all surgeries. To account for antibiotic concentration, we also divided maximum and cumulative doses by body weight for all individuals for whom we had body weight data. History of long-term antibiotic treatment was defined as treatments that were received prior to surgery and documented in the orthopedic records. Data regarding history of gastric resection and regular intake of aspirin before surgery were also recorded.

The anti-infectious prophylaxis used was determined by standardized local protocols. The treatments included several types of antibiotics (amoxicillin, ampicillin, benzyl penicillin, phenoxymethyl penicillin, tetracycline, cephalosporine, cloxacillin, meropenem, gentamicin, and clindamycin), among which cloxacillin was the most frequently used (83% of treatment courses; 65% of all cohort members). Most treatments consisted of single drugs, and some treatments consisted of combinations. A number of patients (21%) received no antibiotics; during certain periods, many clinics had not yet introduced prophylactic antibiotic treatment or had replaced it by use of a sterile operation box. We tested *in vitro* the susceptibility of two strains of *H. pylori* to the 10 antimicrobial agents used among our study persons (E-test; Biodisk AB, Solna, Sweden). The strains were sensitive to all of the tested agents, with minimal inhibitory concentration values between <0.016 and 0.5 μg/ml (cancer strain) and <0.016–1.5 μg/ml (strain NCTC11637). The similar efficacy observed for all of the agents precluded any efficient ranking scheme. To facilitate comparisons of different antibiotics and to allow summation of more than one drug, we constructed new dose variables by dividing the recorded doses by drug-specific DDDs[3] (11). The DDD for a drug is established on the basis of the assumed average dose per day for the drug used for its main indication in adults. When a combination of drugs was used, maximum and cumulative DDDs were added for the component drugs.

Anti-*H. Pylori* IgG Seroreversion (Cohorts II and III). Analyses of anti-*H. pylori* IgG in serum samples collected before and after hip replacement surgery were done using a separate cohort (cohort II) of patients undergoing hip replacement surgery between 1986 and 1995 at the Department of Orthopedics (Sahlgrenska-Östra University Hospital, Gothenburg, Sweden). At surgery, all patients had been given a standard prophylactic antibiotic treatment of i.v. cloxacillin (4 grams) on day 1 and oral dicloxacillin (3 grams) on days 2 and 3. We obtained a total of 121 matching pairs of sera from patients who were *H. pylori* positive before surgery (56 men and 65 women). The samples were assayed for anti-*H. pylori* IgG by an ELISA technique (HM-CAP; Enteric Products, Inc., Westbury, NY) with a sensitivity and specificity of 94–98% (12) and 92–97% (13), respectively. The criteria for *H. pylori* positivity and negativity were determined according to the manufacturer's instructions. To study atrophic gastritis as a possible determinant for seroreversion, we analyzed pepsinogen A (PGI Gastroset; Orion) as an indicator for presence of this condition (14–16). Pepsinogen A concentrations below 25 μg/liter were regarded as significant chronic atrophic gastritis (17).

Finally, to study the rate of spontaneous seroreversion in the background population, we analyzed sera from a cohort (cohort III) of 455 men, all born in 1913, living in the city of Gothenburg (18). They were tested in 1980 and 1988, using the same assay used for the hip replacement cohort (cohort II). Local ethical committees in Gothenburg and Uppsala have approved the studies.

Statistical Analyses. For the analyses of the nested case-control study (cohort I), maximum dose and cumulative dose were categorized as below or above the median, based on the distribution among both cases and controls (19). Aspirin use was dichotomized (regular *versus* not regular). Histories of long-term antibiotic use and of gastric resection were also treated as dichotomous variables (yes/no). Data were modeled with conditional logistic regression. For the analyses of the second cohort (cohort II), data were modeled with unconditional logistic regression. Maximum likelihood estimates of the OR were determined in both univariate and multivariate models, with the 95% CIs presented as indicators of statistical precision. We tested for linear trend by constructing ordinal variables through assigning consecutive integers to consecutive levels of the categorized variables (Wald's test). All *P*s are two-tailed.

RESULTS

Table 1 shows the distribution of cases of gastric cancer and individually matched controls (cohort I) according to age, gender, indication for index surgery, number of recorded orthopedic surgeries during follow-up (including the index surgery), and history of gastric resection, as well as the mean follow-up time for cases and controls. The majority of cases were male (57%), whereas the majority of controls were female (62%). Otherwise, there were no striking differences between cases and controls with respect to any of the other variables.

Table 2 presents the distribution of cases and matched controls according to the studied variables, as well as ORs with 95% CIs for the association between these variables and gastric cancer. Controlling for gender, age, gastric resection, and regular use of aspirin rendered results similar to the crude model. A history of long-term antibiotic treatment before the index surgery was associated with a significant 70% decrease in gastric cancer risk. Having received any prophylactic antibiotic treatment conferred a 30% reduction in risk, but the CIs included unity. Both maximum and cumulative antibiotic doses per kilogram of body weight were inversely associated with risk, but the tests for linear trend were nonsignificant. We analyzed different types of antibiotics separately (data not shown), and, although hampered by small numbers, we found similar results for all subgroups. A nonsignificant inverse association was also observed for regular use of aspirin before surgery. Male sex (OR, 2.2; 95% CI, 1.5–3.3) and history of gastric resection (OR, 2.3; 95% CI, 1.0–5.0) were statistically significant risk factors for gastric cancer.

We further assessed the effect of exposure to prophylactic antibiotics, stratified by length of follow-up time (Table 3). The protective effect of prophylactic antibiotic use tended to be stronger among patients followed for a longer period of time: the OR was 0.6 for those

Table 1 *Characteristics of 174 case patients with gastric cancer and 462 individually matched control subjects without gastric cancer in the Swedish cohort of 39,154 patients undergoing hip replacement surgery*

Characteristic	No. of cases (% of total)	Controls
Age (yrs)		
<65	37 (21)	100 (22)
65–69	37 (21)	100 (22)
70–74	49 (28)	137 (30)
≥75	51 (29)	125 (27)
Gender		
Female	74 (43)	286 (62)
Male	100 (57)	176 (38)
Indication for index surgery[a]		
Osteoarthritis	114 (66)	307 (66)
Acute fracture	8 (5)	31 (7)
Late sequelae after fracture	48 (28)	103 (22)
Rheumatoid arthritis	7 (4)	22 (5)
Other	6 (3)	16 (3)
No. of surgeries[b]		
1	134 (77)	361 (78)
2	33 (19)	85 (18)
≥3	7 (4)	16 (3)
History of gastric resection		
No	159 (91)	447 (97)
Yes	15 (9)	15 (3)
Mean follow-up time (years)	5.37	5.40
Median duration of antibiotic treatment (days)	8	9

[a] More than one indication was allowed, thus numbers exceed the total.
[b] The number of surgeries during follow-up includes index surgery.

[3] The abbreviations used are: DDD, defined daily dose; OR, odds ratio; CI, confidence interval; ELISA, enzyme-linked immunosorbent assay.

Table 2 *Conditional logistic regression-derived crude and adjusted ORs and 95% CIs for the association between the studied variables and gastric cancer*

Variables	Number		Crude		Adjusted	
	Cases (n = 174)	Controls (n = 462)	OR	95% CI	OR[a]	95% CI
Long-term antibiotic treatment before surgery						
No	167	414	Ref.[c]		Ref.	
Yes	7	48	0.3	0.2–0.8	0.3	0.1–0.7
Prophylactic antibiotic treatment[b]						
No	44	90	Ref.		Ref.	
Yes	129	367	0.7	0.4–1.1	0.7	0.5–1.1
Maximum prophylactic antibiotic dose per day[b]						
None	44	90	Ref.		Ref.	
Below median (3 DDD)	66	178	0.7	0.5–1.2	0.7	0.4–1.2
Above median	62	183	0.7	0.4–1.1	0.7	0.4–1.2
Weight-adjusted maximum prophylactic antibiotic dose[b]						
None	24	48	Ref.		Ref.	
Below median (0.04 DDD/kg)	52	125	0.7	0.4–1.4	0.7	0.3–1.4
Above median	43	133	0.5	0.2–1.0	0.5	0.2–1.1
						P for trend = 0.13
Cumulative prophylactic antibiotic dose[b]						
None	44	90	Ref.		Ref.	
Below median (15.5 DDD)	59	182	0.7	0.4–1.1	0.7	0.4–1.1
Above median	63	177	0.7	0.4–1.1	0.7	0.4–1.2
Weight-adjusted cumulative prophylactic antibiotic dose[b]						
None	24	48	Ref.		Ref.	
Below median (0.21 DDD/kg)	45	128	0.7	0.3–1.4	0.7	0.3–1.4
Above median	45	130	0.5	0.3–1.1	0.6	0.3–1.2
						P for trend = 0.29
Regular use of aspirin before surgery						
No	133	334	Ref.		Ref.	
Yes	41	128	0.8	0.5–1.2	0.8	0.5–1.2

[a] Adjusted for gender, age, history of gastric resection, and regular use of aspirin.
[b] Frequencies do not sum to total because of missing data.
[c] Ref., referent group.

followed for ≥5 years, compared with an OR of 0.8 for those followed for <5 years. Among 9 cases and 17 controls followed for more than 12 years, the OR was 0.4 (95% CI, 0.0–2.8). In contrast, the protective effect of regular aspirin use seemed limited to those followed for <5 years.

We explored the joint effect of antibiotics and aspirin (Table 4) and found that each of these factors reduced the risk of gastric cancer in the absence of the other. The effects were strong, with about 40–60% reductions in risk observed for prophylactic antibiotic treatment and aspirin use. If both factors were present, however, the risk was not further reduced.

The cohort from which we had obtained serum samples (cohort II) was followed for a mean time of 3.9 years (range, 1.1–9.9 years; mean time of 3.5 years among those who seroreverted and 4.1 years among those who remained seropositive). In both groups, the mean age was 70 years (range, 44–87 years). During the study follow-up period, the cumulative incidence of seroreversion was 14% (17 of 121 subjects).

Table 3 *Conditional logistic regression-derived ORs*[a] and 95% CIs for the association of prophylactic antibiotic treatment, regular use of aspirin and gastric cancer, stratified by follow-up time

Years of follow-up		No. of Cases	No. of Controls	OR	95% CI
A. Prophylactic antibiotic treatment[a]					
<5	No	23	51	Ref.[c]	
	Yes	65	177	0.8	0.4–1.4
≥5	No	21	39	Ref.	
	Yes	64	190	0.6	0.3–1.2
B. Regular use of aspirin[b]					
	No	71	166	Ref.	
<5	Yes	17	66	0.6	0.3–1.1
≥5	No	62	168	Ref.	
	Yes	24	62	1.0	0.6–1.9

[a] Adjusted for gender, age, history of gastric resection, and regular use of aspirin.
[b] Adjusted for gender, age, history of gastric resection, and prophylactic antibiotic treatment.
[c] Ref., referent group.

Within this cohort (cohort II), atrophic gastritis was associated with increased odds of seroreversion (OR, 3.5; 95% CI, 1.05–13.4). In our control population (cohort III), the 8-year cumulative incidence of spontaneous seroreversion was 11% (42 of 366 subjects). Calculation of annual seroreversion rates showed a reversion rate of 3.6% per year among those treated with prophylactic antibiotics (cohort II), compared with a corresponding rate of 1.4% per year among those in the reference group (cohort III).

DISCUSSION

Our data lend indirect support to the hypothesis that treatment with antibiotics at a fairly advanced age is associated with a reduced gastric cancer risk. Gastric cancer risk appeared to decrease with increasing follow-up time, which is biologically plausible. Because *H. pylori* is thought to be an early-stage carcinogen, the latency between its critical action and cancer diagnosis is likely to be long, and any effect of eradication on cancer occurrence would be expected to increase with time. The rate of *H. pylori* antibody disappearance observed in a cohort of patients undergoing hip replacement surgery (cohort II) was slightly but not substantially higher than that in the background population (cohort III). However, the use of prophylactic antibiotic treatment has varied over time; high doses used in earlier years (up to 12 grams/day) have subsequently been modified to lower doses (2–4 grams/day). Hence, the cohort from which we obtained serum samples (cohort II) was most likely exposed to lower doses of prophylactic antibiotics than the original cohort (cohort I) because patients in the original cohort underwent surgery up to 30 years before patients in the second cohort. The reduction in prophylactic treatment over time could thus explain the absence of a marked effect on *H. pylori* antibody disappearance. Our comparison group (cohort III) was similar to the *H. pylori*-tested cohort (cohort II) with regard to age and study area but differed with regard to gender composition (men only) and length of follow-up time (8 years *versus* a mean of 3.9 years).

Table 4 *Evaluation of the joint impact of use of aspirin and prophylactic antibiotics on gastric cancer risk: adjusted[a] conditional logistic regression-derived ORs and 95% CIs*

	Maximum antibiotic dose		
Aspirin	No	Below median	Above median
No	1.00 (Ref.)[b]	0.6 (0.3–1.0)	0.6 (0.3–1.1)
Yes	0.4 (0.2–1.2)	0.6 (0.3–1.2)	0.5 (0.2–1.0)

[a] Adjusted for gender, age, and history of gastric resection.
[b] Data are given as OR (95% CI). Ref., referent group.

Comparing the cumulative seroreversion rates, it is noteworthy that the reversion rate among those treated with prophylactic antibiotics (cohort II) presumably peaked in connection with the surgery at entry, whereas the spontaneous reversion rate in the comparison cohort (cohort III) was most likely constant over time. A Danish population-based study has reported an 11-year cumulative seroreversion rate of 7.7% (20). Comparable data regarding spontaneous disappearance of *H. pylori* infection are otherwise limited. Two smaller longitudinal studies have presented annual seroreversion rates of 1.6% (21) and 0.6% (22).

However, a fairly small increase in seroreversion may be sufficient to produce the observed risk reduction if loss of *H. pylori* infection preferentially occurs in high-risk individuals. The treatments most commonly used for prophylactic purposes in hip replacement surgery are not normally those prescribed against *H. pylori*. Because *H. pylori* is sensitive to almost all types of antimicrobial agents *in vitro* (23, 24), the frequent treatment failures with simple antibiotic regimens *in vivo* are probably due to local factors in the stomach rather than bacterial resistance. Atrophic gastritis is associated with an elevated gastric pH, which may amplify the effect of a normally less potent antibiotic (25–27). Atrophic gastritis, which is itself a likely key step in gastric carcinogenesis associated with a marked increase in the risk of gastric cancer (28–30), may paradoxically generate the possibility of eradication from normally ineffectual antibiotics. Although loss of the infection in advanced atrophic gastritis is generally perceived as a marker of imminent cancer development, we speculate that there is a window of time between the establishment of atrophy and the point of no return in the carcinogenic pathway during which eradication is both facilitated and efficient in halting the carcinogenic process.

Our finding of a negative association between gastric cancer and regular use of aspirin is consistent with earlier studies (31–33). Although based on small numbers, our study suggested that regular aspirin use modified the effect of antibiotics; that is, among users of aspirin, no additional protection was afforded by antimicrobial therapy. Hypothetically, these treatments might work through the same biological mechanism, by disrupting, perhaps at different levels, the *H. pylori*-gastric cancer pathway.

Although more than 300,000 person-years at risk were surveyed in the cohort (cohort I), the number of observed cancer cases and hence the statistical precision in the nested case-control study were insufficient to rule out chance as an explanation for our findings with reasonable confidence. Indeed, our findings are a reminder of the immense sample size and long follow-up required to demonstrate a statistically significant risk reduction in a prevention trial. A strong *a priori* hypothesis and the biological plausibility of our findings may, to some extent, outweigh precision weaknesses.

Because our case-control study was nested in a well-defined cohort, the validity of the underlying cohort study is preserved. Hence selection bias is minimized, and differential misclassification is precluded by the prospective nature of the data collection. Furthermore, information bias was controlled by blinding of data abstractors. Allocation to antibiotic treatment regimens was not individualized but followed standardized local protocols. Therefore, confounding by indication or by other factors linked to the individual is unlikely. The cases and controls may have been prescribed antibiotics at medical departments other than those under surveillance. We were unable to capture such treatment episodes. The resulting misclassification of exposure should be nondifferential and thus lead to underestimation of the true effect (34).

Besides reports of regression of low-grade MALT lymphoma after *H. pylori* eradication (35), there have been a few clinical studies that indirectly indicated that *H. pylori* eradication might prevent gastric cancer (36, 37). Randomized chemoprevention trials are ongoing but have experienced difficulties in attaining high rates of permanent *H. pylori* eradication (38, 39). Therefore, conclusive evidence of a cancer-protective effect of *H. pylori* eradication may not become available in the near future. In the absence of studies capable of directly examining whether *H. pylori* eradication decreases the risk of gastric cancer, our study provides some supplementary suggestive evidence.

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