Is Helicobacter pylori infection a necessary condition for non-cardia gastric cancer ?

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Background

Although the association between *Helicobacter pylori* infection and gastric cancer is well established, this association might have been underestimated in epidemiologic studies due to possible clearance of the infection in the course of disease development. [1]

Aim of the study

We specifically addressed this hypothesis in a re-analysis of a large case control study, in which various exclusion criteria were employed to minimize potential bias from this source.[2]

Methods

68 patients with gastric cancer and 360 controls were recruited in a population-based case-control study in Saarland/Germany between 11/1996 and 2/1998. Personal interviews were conducted and serum samples were taken during first hospitalization due to the cancer. Serum samples were analysed for *H pylori* specific IgG antibodies by ELISA (GAP, Bio-Rad, München, Germany) and for antibodies against the CagA antigen by Western blot (AID, Strasberg, Germany). Cases were compared to controls with respect to serological evidence of *H pylori* infection and CagA positivity in the entire sample and after (consecutive) exclusion of subgroups among whom *H pylori* test results might not adequately indicate previous *H pylori* exposure.

Results

Seroprevalence of *H pylori* infection was higher among cases than among controls (see table 1), resulting in odds ratios (ORs) of 2.3 and 3.7 for total and non-cardia gastric cancer, respectively (table 2). The ORs were higher for CagA positive than for CagA negative infections.

After exclusion of 8 patients whose serum samples were obtained more than 90 days after gastrectomy, 17 patients with advanced (T4) gastric cancer, one patient and 22 controls who were seronegative according to IgG ELISA, but who were CagA positive according to Westernblot, and another 3 patients and 54 controls with a borderline *H pylori* IgG result, only 2 seronegative patients were left among 39 remaining gastric cancer patients, and no single seronegative patient was left among 32 remaining cases with non-cardia gastric cancer. By contrast, there remained 58 seronegative subjects among 285 controls. As a result, the OR for total gastric cancer was increased to 5.0 for all *H pylori* infections, and to 7.2 for CagA positive infections. The OR for non-cardia gastric cancer increased from 3.7 to 18.3 for all *H pylori* infections, and from 5.7 to 28.4 for CagA positive *H pylori* infections after application of the first three exclusion criteria, and to infinity after additional application of the fourth exclusion criterium.

Conclusion

The *H pylori* – gastric cancer relationship may be much stronger than previously thought and *H pylori* infection may even be a (close to) necessary condition for development of non-cardia gastric cancer.

Table 1: Numbers (proportions) of cases and controls without *H pylori* infection according to IgG ELISA (HP-),and with CagA negative and CagA positive *H pylori* infection (HP+) in the entire sample and after exclusion of subjects in whom interpretation of *H pylori* serology may be uncertain

	all patients with gastric cancer			non-cardia gastric cancer patients			controls		
	HP-	HP+		HP-	HP+		HP-	HP+	
Sample		CagA-	CagA+		CagA-	CagA+		CagA-	CagA+
All patients	15 (22%)	22 (32%)	31 (46%)	9 (16%)	18 (32%)	30 (53%)	133 (37%)	143 (40%)	84 (23%)
Exclusions (consecutive):									
>90 days after gastrectomy	10 (17%)	20 (33%)	30 (50%)	6 (12%)	16 (31%)	29 (57%)	133 (37%)	143 (40%)	84 (23%)
T4 gastric cancer	6 (14%)	16 (37%)	21 (49%)	2 (6%)	12 (35%)	20 (59%)	133 (37%)	143 (40%)	84 (23%)
Neg. Hp IgG ELISA, CagA+	5 (12%)	16 (38%)	21 (50%)	1 (3%)	12 (36%)	20 (61%)	112 (33%)	143 (42%)	84 (25%)
Borderline Hp IgG result	2 (5%)	16 (41%)	21 (54%)	0 (0%)	12 (38%)	20 (63%)	58 (20%)	143 (50%)	84 (29%)

Table 2: Odds ratios with 95% confidence intervals, adjusted for age and gender, for the association between *H pylori* infection and gastric cancer derived from the entire sample and after exclusion of subjects in whom interpretation of *H pylori* serology may be uncertain

	gastric cancer, any location			non-cardia gastric cancer only		
Sample	overall	CagA-	CagA+	overall	CagA-	CagA+
All patients	2.3 1.2-4.3	1.5 0.8-3.1	3.4 1.7-6.7	3.7 1.7-7.9	2.3 1.0-5.3	5.7 2.6-12.8
Exclusions (consecutive):						
> 90 days after gastrectomy	3.3 1.6-6.8	2.1 1.0-4.8	5.0 2.3-10.8	5.3 2.2-13.0	3.1 1.2-8.3	8.5 3.3-21.5
T4 gastric cancer	3.8 1.6-9.3	2.6 1.0-7.0	5.6 2.2-14.6	10.6 2.5-45.5	6.5 1.4-29.7	16.7 3.8-73.4
Neg. Hp IgG ELISA, CagA+	3.9 1.5-10.3	2.7 1.0-7.7	5.7 2.1-15.9	18.3 2.4-136.7	11.1 1.4-87.6	28.4 3.7-217.1
Borderline Hp IgG result	5.0 1.2-21.4	3.5 0.8-15.8	7.2 1.6-32.2	∞	∞	∞

References

1 Ekström AM, Held M, Hansson L-E, et al. *Helicobacter pylori* in gastric cancer established by CagA immunoblot as a marker of past infection. Gastroenterology 2001; 121: 784-91.
2 Brenner H, Arndt V, Stegmaier C, Ziegler H, Rothenbacher D. Is *Helicobacter pylori* infection a necessary condition for non-cardia gastric cancer ? Am J Epidemiol (in press).