

Is *Helicobacter pylori* Infection a Necessary Condition for Noncardia Gastric Cancer?

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Although the association between *Helicobacter pylori* infection and gastric cancer is well established, this association might have been underestimated in epidemiologic studies because of possible clearance of the infection in the course of disease development. The authors addressed this hypothesis in a case-control study from Saarland, Germany (68 cases first diagnosed between 1996 and 1998 and 360 controls), with serologic assessment of *H. pylori* infection in which various exclusion criteria were used to minimize potential bias from this source. Joint application of three such exclusion criteria (blood sample taken more than 90 days after gastrectomy, advanced (T4) gastric cancer, and CagA positivity in Western blot analysis despite a negative result in anti-*H. pylori* immunoglobulin G enzyme-linked immunosorbent assay) increased the odds ratio of noncardia gastric cancer from 3.7 (95% confidence interval (CI): 1.7, 7.9) to 18.3 (95% CI: 2.4, 136.7) for any *H. pylori* infection and from 5.7 (95% CI: 2.6, 12.8) to 28.4 (95% CI: 3.7, 217.1) for CagA-positive *H. pylori* infections. Furthermore, there was no single *H. pylori*-negative patient out of 32 patients with noncardia gastric cancer left after additional exclusion of subjects with borderline levels in immunoglobulin G enzyme-linked immunosorbent assay. The *H. pylori*-gastric cancer relation may be much stronger than previously thought, and *H. pylori* infection may even be a (close to) necessary condition for development of noncardia gastric cancer.

case-control studies; *Helicobacter pylori*; stomach neoplasms

Abbreviations: CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; IgG, immunoglobulin G.

Since the publication of the first landmark reports at the beginning of the 1990s (1–4), numerous studies have confirmed an increased risk of gastric cancer, in particular noncardia gastric cancer, among subjects infected with the gastric bacterium *Helicobacter pylori*. In several meta-analyses, the risk of gastric cancer was estimated to be two- to threefold elevated among infected compared with uninfected people (5–9). However, estimates of relative risk varied by cancer site and by characteristics of both the host and the infectious agent. Higher relative risks were consistently found for noncardia gastric cancer and, at least in Western countries, infections with cytotoxin-associated gene A (*cagA*)-positive strains of *H. pylori*. Furthermore the relative risks were found to decrease with age (5, 8). In case-control studies in which the diagnosis of *H. pylori* infection was made based on tests used at the time of enrollment in the

study (i.e., after diagnosis of gastric cancer), a stronger association was found for early than for advanced gastric cancer (5), whereas in case-control studies nested within cohort studies, relative risks were stronger if blood samples were collected many years before cancer diagnosis (8).

Taken together, these patterns are consistent with the hypothesis that the *H. pylori*-gastric cancer association may have been underestimated in epidemiologic studies because of selective misclassification of the infection status within the relevant time window (i.e., at the time when carcinogenesis was initiated) among patients with gastric cancer, particularly among older patients, patients with more advanced disease, and patients with CagA-positive infections. These patients generally have more severe mucosal atrophy and intestinal metaplasia in the stomach as disease progresses, conditions that increase the chance of clearance of the

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bacteria from the gastric mucosa a long time after patho-physiologic changes possibly leading to gastric cancer have been initiated.

In contrast to attempts to increase the precision of the estimates of the *H. pylori*-gastric cancer association by meta-analyses, attempts to increase the validity of the estimates by overcoming and correcting for the putative underestimation of the association due to underdetection of *H. pylori* infection have been scarce. Such underestimation may be substantial: In one recent case-control study from Sweden (10), the adjusted odds ratio of serologically defined *H. pylori* infection for noncardia gastric cancer increased from 2.2 to 21.0, if subjects who were negative by immunoglobulin G (IgG) enzyme-linked immunosorbent assay (ELISA) but CagA positive by immunoblot analysis were removed from the reference group of seronegative subjects (a pattern that might be indicative of past infection with *cagA*-positive *H. pylori* strains, as existing clinical data indicate that anti-CagA antibodies persist longer after loss of the infection than specific IgG antibodies detected by conventional ELISA (11)). These intriguing findings suggest that more detailed epidemiologic analyses aimed at overcoming potential bias due to underdetection of *H. pylori* infection may give a more valid estimate of the *H. pylori*-gastric cancer relation. Following these considerations, we carried out a detailed reanalysis of a large case-control study on the association of *H. pylori* infection with gastric cancer conducted in Germany.

MATERIALS AND METHODS

Study design and study population

This analysis is based on data of a statewide, population-based study on risk factors, patterns of the diagnostic process, and prognosis conducted among patients with various forms of cancer in Saarland, Germany. Details of the design of this study have been reported elsewhere (12). Briefly, all patients with a first diagnosis of gastric cancer, colorectal cancer, or breast cancer between November 1996 and February 1998 who were aged 80 years or less were eligible for participation contingent on written informed consent. Patients were recruited during first hospitalization due to their cancer by 34 of 36 pertinent hospitals participating in the study in Saarland. Among the eligible subjects reported to the study center by these hospitals, 2 percent died before an interview could be conducted, and another 3 percent refused to participate.

In this case-control analysis, patients with a first diagnosis of histologically verified gastric cancer (cases) are compared with respect to *H. pylori* infection with patients with a first diagnosis of histologically verified colorectal cancer, who served as controls. This approach has also been used in two previous reports that had specifically addressed the joint impact of *H. pylori* infection and family history of gastric cancer (13) and smoking (14) on gastric cancer risk.

Data collection

Data collection included personal standardized interviews, collection of medical information from the hospital charts, and drawing of blood samples. All interviews were conducted by a team of four trained interviewers. Most interviews could be realized during hospitalization of the patients, typically a few days after surgery, but in some cases interviews had to be postponed until after discharge and, in a few cases, were possible only several weeks to months after surgery. Following the interviews, nonfasting blood samples were obtained by venipuncture from 82 percent of the patients who agreed to this additional component of the study. In addition, detailed information on clinical features, including the exact location, stage, and histology of the tumors, was obtained from hospital charts and pathology reports.

Serum samples were stored at -80°C and analyzed for the presence of IgG antibodies to *H. pylori* by an ELISA (GAP Assay; Bio-Rad Laboratories Diagnostics Group, München, Germany). According to the manufacturer's instructions, levels above 20 units/ml were considered positive, and levels below 12.5 units/ml were considered negative. Individuals with borderline levels between 12.5 and 20 units/ml (17 percent of all subjects) were treated as negative in the initial statistical analyses (which reflects common practice in serology-based studies of the *H. pylori*-gastric cancer association) and excluded in subsequent alternative statistical analyses (see below). The Bio-Rad GAP Assay IgG test kit has been extensively evaluated, and it performed well compared with other commercial kits (15). The sera were further analyzed for the presence of antibodies to the CagA antigen using a commercial Western blot test (*H. pylori* Western blot; Autoimmun Diagnostika GmbH (AID), Strasberg, Germany). All laboratory analyses were carried out in blinded fashion by trained personnel in a central laboratory as previously described (13). However, in contrast to our previous work, in which results of the Western blot analysis had been available only among patients who were positive in the IgG ELISA (13, 14), we meanwhile extended the Western blot analyses to all cases and controls.

Statistical analysis

We compared the seroprevalence of *H. pylori* infection between cases and controls according to the result of the Bio-Rad GAP Assay test. Among seropositive subjects, a further distinction was made between CagA-positive and CagA-negative subjects. The association between the serostatus of *H. pylori* infection and the risk of gastric cancer was quantified by odds ratios and their 95 percent confidence intervals after adjustment for age and gender by multiple logistic regression. Because of the small number of subjects in some patient subgroups, logistic regression models using conditional rather than unconditional maximum likelihood estimation were used (16). All analyses were carried out using SAS statistical software (SAS Institute, Inc., Cary, North Carolina).

To address potential underestimation of the *H. pylori*-gastric cancer association due to loss of the infection during

the course of disease, we repeated the analyses after excluding, both separately (one at a time) and sequentially (in a cumulative manner), the following subgroups of study participants for whom *H. pylori* test results might not adequately indicate previous *H. pylori* exposure:

1. Patients with gastric cancer who could only be interviewed and whose blood samples were taken more than 3 months after surgery and patients who had developed gastric cancer after previous gastrectomy. These patients were excluded because seroreversion might be expected in the long run after total or subtotal gastrectomy, even though the prevalence of the infection appears to remain high in the absence of specific treatment (17, 18).
2. Patients with advanced (T4) gastric cancer, which often goes along with severely atrophic epithelium or areas of intestinal metaplasia, conditions under which *H. pylori* may not be able to survive (19).
3. Cases and controls who were seronegative according to the ELISA test for anti-*H. pylori* IgG antibodies but who were found to be CagA positive in the Western blot. Such a pattern might reflect recent clearance of *H. pylori* infection (e.g., due to severe gastric atrophy), because the immune response against the CagA antigen may persist longer than the antibodies detected by IgG ELISA (11).
4. Cases and controls with borderline levels (12.5–20.0 units/ml) in the IgG ELISA, which might again reflect recent clearance of the infection (e.g., due to severe gastric atrophy). This suggestion is supported by recent work (20), which showed that older subjects with borderline IgG levels have a particularly high risk of gastric cancer.

Because previous studies have suggested that *H. pylori* primarily or even exclusively affects the risk of noncardia gastric cancer (5), all analyses were repeated including patients with noncardia gastric cancer in the case group only.

RESULTS

Overall, 68 cases and 360 control patients who agreed to give a blood sample and in whom *H. pylori* serostatus could be determined were included. The median ages were 64 years and 66 years among cases and controls, respectively. About 60 percent of both cases and controls were males; 98.4 percent of study participants were of German nationality.

The cases included two patients who had developed cancer at the anastomosis after previous gastrectomy and 11 patients with cancer at the gastroesophageal junction ($n = 1$) or the cardia ($n = 10$). Only 18 percent and 21 percent of the cases were diagnosed at stage T1 and stage T2, respectively, whereas 26 percent of the cases were diagnosed with a stage T4 cancer. All but two gastric cancer patients underwent gastric surgery, and in 76 percent of these patients, interview and venipuncture could be realized before or within 30 days after gastric surgery. There were seven cases (11 percent),

however, who could only be interviewed more than 3 months after gastric surgery.

The majority of both cases and controls in the total sample were seropositive for *H. pylori* infection according to the IgG ELISA, but the prevalence was higher among cases (78 percent) than among controls (63 percent) (table 1). In particular, the proportion of subjects with CagA-positive infections was higher among cases (46 percent) than among controls (23 percent), and the differences were even larger when the case group was restricted to patients with noncardia cancer only.

The differences in overall seroprevalence (regardless of CagA status) result in odds ratios of 2.3 (95 percent confidence interval (CI): 1.2, 4.3) and 3.7 (95 percent CI: 1.7, 7.9) for total gastric cancer and for noncardia gastric cancer, respectively (table 2). The corresponding odds ratios for CagA-positive infections are 3.4 (95 percent CI: 1.7, 6.7) and 5.7 (95 percent CI: 2.6, 12.8), respectively, considerably higher than those for CagA-negative infections, which are 1.5 (95 percent CI: 0.8, 3.1) and 2.3 (95 percent CI: 1.0, 5.3), respectively. These odds ratios remained essentially unchanged when additional potential confounding variables, including smoking and level of school education, were controlled for in subsequent analyses.

After exclusion of eight patients with gastric cancer whose serum samples were obtained more than 90 days after gastrectomy or who had developed gastric cancer after previous gastrectomy, five of whom were seronegative, the seroprevalence increased to 83 percent among all gastric cancer patients and to 88 percent among noncardia gastric cancer patients (table 1). As a consequence, the overall odds ratios for *H. pylori* infection increased from 2.3 to 3.3 for total gastric cancer and from 3.7 to 5.3 for noncardia gastric cancer. The odds ratios for CagA-positive infections increased from 3.4 to 5.0 and from 5.7 to 8.5, respectively (table 2). Separate (one at a time) exclusion of 18 (26 percent) patients with advanced (T4) gastric cancer, of two cases and 21 controls who were seronegative according to IgG ELISA but who were CagA positive according to Western blot, or of eight cases and 65 controls with borderline levels of IgG led to a somewhat less pronounced increase in the odds ratios for noncardia cancer and did not materially affect the odds ratios for total gastric cancer.

However, after simultaneous application of the four exclusion criteria, only two seronegative patients were left among 39 remaining gastric cancer patients, corresponding to a seroprevalence of 95 percent. By contrast, there remained 58 of 285 controls who were seronegative, corresponding to a seroprevalence of 80 percent (table 1). As a result, the overall odds ratio for total gastric cancer was strongly increased to 5.0 (95 percent CI: 1.2, 21.4) for all *H. pylori* infections and to 7.2 (95 percent CI: 1.6, 32.3) for CagA-positive infections (table 2). The odds ratio for noncardia gastric cancer increased from 3.7 (95 percent CI: 1.7, 7.9) to 18.3 (95 percent CI: 2.4, 136.7) for all *H. pylori* infections and from 5.7 (95 percent CI: 2.6, 12.8) to 28.4 (95 percent CI: 3.7, 217.1) for CagA-positive *H. pylori* infections, even after application of only the first three of the four exclusion criteria. A closer look at the single *H. pylori*-negative patient with noncardia gastric cancer who was left after application

TABLE 1. Numbers and percentages of cases and controls who were HP-* and HP+* in the entire sample and after exclusion of defined subgroups of patients in whom interpretation of *Helicobacter pylori* serology may be uncertain, Saarland, Germany, 1996–1998

Sample	All patients with gastric cancer			Noncardia gastric cancer patients†			Controls		
	HP–	HP+		HP–	HP+		HP–	HP+	
		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 (one at a time)									
>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¶	11 (22)	17 (34)	22 (44)	5 (13)	13 (33)	21 (54)	133 (37)	143 (40)	84 (23)
HP–, CagA+‡	13 (20)	22 (33)	31 (47)	7 (13)	18 (33)	30 (55)	112 (33)	143 (42)	84 (25)
Borderline IgG* result	7 (12)	22 (37)	31 (52)	4 (8)	18 (35)	30 (58)	68 (23)	143 (48)	84 (28)
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)
HP–, CagA+	5 (12)	16 (38)	21 (50)	1 (3)	12 (36)	20 (61)	112 (33)	143 (42)	84 (25)
Borderline IgG result	2 (5)	16 (41)	21 (54)	0 (0)	12 (38)	20 (63)	58 (20)	143 (50)	84 (29)

* HP–, without *H. pylori* infection according to immunoglobulin G enzyme-linked immunosorbent assay; HP+, with CagA-negative or CagA-positive *H. pylori* infection; IgG, immunoglobulin G.

† Excluding one patient with gastric cancer at the gastroesophageal junction and 10 patients with cardia cancer.

‡ Numbers in parentheses, percentage.

§ Exclusion of gastric cancer patients who were interviewed more than 90 days after surgery or who developed gastric cancer after previous gastrectomy.

¶ Exclusion of gastric cancer patients with T4 cancers.

Exclusion of gastric cancer patients and controls who were IgG negative in enzyme-linked immunosorbent assay and CagA positive in Western blot analysis.

of these exclusion criteria revealed that this patient, a man aged 60 years, also had quite advanced disease (T3) and a borderline value in the IgG ELISA. Hence, after application of this additional exclusion criterion, there was no *H. pylori*-negative patient left among the remaining 32 cases with noncardia gastric cancer.

DISCUSSION

In this in-depth analysis of a case-control study, the proportion of seronegative subjects among cases with gastric cancer strongly decreased if the sample was restricted to patients in whom possible loss of the infection as a consequence of gastric atrophy (and therefore misclassification of previous *H. pylori* exposure) was less likely. As a consequence, much stronger associations of *H. pylori* infection with gastric cancer, and particularly noncardia gastric cancer, emerged if such exclusions were made.

Our results are in agreement with previous findings of a stronger *H. pylori*-gastric cancer association in subgroups of patients in whom loss of the infection as a consequence of the disease process itself is less likely, such as younger patients or patients with early gastric cancer (5, 8). However, in previous analyses such factors were mostly considered one at a time only, and our third criterion, *H. pylori* seronegativity despite CagA positivity, has been applied in only one recent study from Sweden (10). In that study, patients with previous gastrectomy were also excluded, and blood had

been taken preoperatively among all participants (an even more stringent criterion than our first exclusion criterion).

In both the Swedish study and our study, the results of a standard analysis without exclusions of subjects with possible disease-induced loss of infection yielded odds ratios that are very similar to those obtained in many other studies and in pertinent meta-analyses, but the odds ratios were much higher if a consequent approach was taken to exclude such subjects. After exclusion of IgG ELISA-negative, CagA-positive subjects from the reference group, the odds ratio for noncardia gastric cancer rose to 21.0 in the Swedish study, a value that is much higher than previously reported estimates and remarkably similar to the estimate of 18.3 obtained in our analysis after application of the first three exclusion criteria (patients with borderline IgG values, our fourth exclusion criterion, were not excluded in the Swedish study). The finding that no single patient among the 32 remaining cases with noncardia gastric cancer was left after application of all four exclusion criteria in our study even raises the question of whether *H. pylori* infection might even be a (close to) necessary cause of noncardia gastric cancer. This suggestion would be supported by a recent cohort study from Japan, in which 36 of 1,246 *H. pylori*-infected subjects, but none of 280 uninfected subjects, developed gastric cancer during a mean follow-up of 7.8 years (21).

However, our study also has limitations. Although it was larger than most single studies reported on the relation of *H. pylori* to gastric cancer to date, the number of patients with gastric cancer was much lower and the confidence intervals

TABLE 2. Odds ratios with 95% confidence intervals, adjusted for age and gender, for the association between *Helicobacter pylori* infection and gastric cancer derived from the entire sample and after exclusion of defined subgroups of patients in whom interpretation of *H. pylori* serology may be uncertain, Saarland, Germany, 1996–1998

Sample	Gastric cancer, any location						Noncardia gastric cancer only*					
	Overall		CagA–		CagA+		Overall		CagA–		CagA+	
	OR†	95% CI†	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
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 (one at a time)												
>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§	2.2	1.1, 4.4	1.5	0.7, 3.4	3.2	1.5, 7.0	4.4	1.7, 11.8	2.7	0.9, 8.0	6.9	2.5, 19.2
HP–, CagA+¶	2.3	1.2, 4.4	1.5	0.7, 3.2	3.4	1.6, 6.9	4.1	1.8, 9.7	2.5	1.0, 6.5	6.4	2.6, 15.5
Borderline IgG† result	2.5	1.1, 5.9	1.7	0.7, 4.3	3.7	1.5, 9.1	4.3	1.5, 12.7	2.6	0.8, 8.3	6.6	2.2, 20.1
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
HP–, 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 IgG result	5.0	1.2, 21.4	3.5	0.8, 15.8	7.2	1.6, 32.2	∞		∞		∞	

* Excluding one patient with gastric cancer at the gastroesophageal junction and 10 patients with cardia cancer.

† OR, odds ratio; CI, confidence interval; IgG, immunoglobulin G.

‡ Exclusion of gastric cancer patients who were interviewed more than 90 days after surgery or who developed gastric cancer after previous gastrectomy.

§ Exclusion of gastric cancer patients with T4 cancers.

¶ Exclusion of gastric cancer patients and controls who were IgG negative in enzyme-linked immunosorbent assay and CagA positive in Western blot analysis.

were much broader than in the meta-analyses that have been done on this issue (5–9). Therefore, replication of our findings in larger samples is required before firm conclusions can be drawn. Furthermore, given the limited numbers of patients retained in the final analyses, the number of covariates that could reasonably be controlled for in multivariable analyses was small. It appears, however, that confounding is not a major issue. The odds ratios hardly changed when additional potential confounding variables were controlled for in the initial model including all study participants.

We used patients with colorectal cancer rather than healthy people as controls. There have been suggestions of a possible weak association between *H. pylori* infection and the risk of colorectal cancer, which would imply that the *H. pylori*-gastric cancer association might still have been underestimated in our study. However, pertinent evidence is inconclusive, and most recent studies have not supported this suggestion (22, 23). Although patients who undergo colorectal surgery frequently receive perioperative antibiotic treatment, this is unlikely to have influenced the serologic results, as antibiotic treatment other than the specific combinations used for *H. pylori* eradication does not seem to have a relevant impact on the persistence of the infection among adults (24) and seroreversion would not be expected in the short run (25). It may also be hypothesized that the serostatus of colorectal cancer patients might be affected by other factors such as cachexia or by decreased immune status (an argument that might also be made for gastric cancer patients), particularly in the case of advanced disease. We therefore carried out additional analyses in which not only

cases but also controls whose blood was taken more than 3 months after surgery, as well as controls with advanced (T4) cancer, were excluded, but these exclusions did not materially alter any of the results. An advantage of the use of colorectal cancer as a control group was that cases and controls were recruited under highly comparable circumstances from the same population and during the same calendar period. It is furthermore reassuring that the point estimates we obtained in the “usual analyses” (without the exclusion of subjects with a potential for misclassification of previous *H. pylori* exposure) were very well in line with the summary odds ratios estimated in meta-analyses from previous studies using population controls. Finally, the *H. pylori* prevalence in our control group was very similar to that reported among comparable age groups from population-based studies conducted in Germany (26–28), which further supports the suggestion that this control group adequately represents the study base that gave rise to the cases.

Although the strength of existing meta-analyses lies in the increasing precision of risk estimates, a major attempt was made in this analysis, like in the Swedish study (10), to increase the validity and to reduce the systematic error from disease-induced changes of infection status to the largest possible extent, which, at the end, almost led back to individual case reviewing. We think that this approach may be a worthwhile complement to the attempt to increase the precision of relative risk estimates based on large numbers of subjects that is made in the meta-analyses. Ideally, of course, both attempts should be combined, and we would like to

encourage combined analyses of previous studies, in which similar approaches to reduce potential misclassification of *H. pylori* infection as the one taken in this study are followed. In particular, it seems that the nested case-control studies, which allow a more direct assessment of the issues addressed in this paper, would be particularly suited for such an investigation. This will require a de novo pooled analysis, however, rather than a meta-analysis of published studies, as the information needed for such an approach is usually not given in pertinent detail in publications.

In summary, our results are in line with previous evidence of a causal relation between *H. pylori* infection and gastric cancer. In agreement with a recent study from Sweden, it suggests, however, that this relation might be much stronger than previously thought (10, 29). Clearly, our findings require corroboration in larger studies or pooled reanalyses of existing studies. If corroborated, they may have far-reaching implications. First, prevention and possibly treatment of *H. pylori* infection might have an even more prominent role in the prevention of gastric cancer than previously thought. Second, the research focus should move from the question of whether and to what extent *H. pylori* infection contributes to noncardia gastric cancer risk to the question of the cofactors responsible for the development of noncardia gastric cancer among the large number of infected people, most of whom do not develop this form of cancer. Such cofactors include characteristics of both the host (13, 14, 29–34) and the infectious agent and may be helpful to focus potential measures of early detection and prevention of gastric cancer (29, 30, 35).

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