

# Gastric Parietal Cell Antibodies, *Helicobacter Pylori* Infection, and Chronic Atrophic Gastritis: Evidence from a Large Population-based Study in Germany

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## Abstract

**Background:** Striking similarities between autoimmune gastritis and *Helicobacter Pylori* (*H. pylori*)-associated gastritis have suggested a potential link between these two pathologic conditions in the progression of chronic atrophic gastritis (CAG); however, evidence has remained conflicting.

**Methods:** Serum pepsinogen I and II, and antibodies against *H. pylori* in general, the cytotoxin-associated gene A protein (CagA) and parietal cells were measured by ELISA in 9,684 subjects aged 50 to 74 years. Antigastric parietal cell antibody (APCA) prevalence was examined in the overall population and according to sex, age, and *H. pylori* serostatus. The association between APCA prevalence and CAG was assessed by logistic regression, overall and according to *H. pylori* status, controlling for potential confounding factors.

**Results:** Overall APCA prevalence was 19.5%. APCA prevalence was strongly associated with CAG, and the association was increasing with increasing severity of CAG. Furthermore, the association between APCA and CAG was even stronger among *H. pylori*-negative subjects [odds ratio (OR) = 11.3; 95% confidence interval (CI): 7.5–17.1] than among *H. pylori*-positive subjects (OR = 2.6; 95% CI: 2.1–3.3).

**Conclusions:** APCA may play a role on the development of gastric atrophy, irrespective of *H. pylori* infection.

**Impact:** Assessment of APCA might be a useful complement to established markers (such as pepsinogens and *H. pylori* antibodies) in screening for CAG. *Cancer Epidemiol Biomarkers Prev*; 22(5); 821–6. ©2013 AACR.

## Introduction

Chronic atrophic gastritis (CAG) is a well-known precursor for gastric cancer (1, 2). Autoimmune gastritis is a special form of CAG, characterized by the presence of circulating autoantibodies against H<sup>+</sup>/K<sup>+</sup>-adenosine triphosphatase (H<sup>+</sup>/K<sup>+</sup>-ATPase), the gastric proton pump located on parietal cells (antiparietal cell antibody, APCA; refs. 3, 4). Following the discovery of *Helicobacter pylori* (*H. pylori*) and the establishment of a causal relationship between *H. pylori* infection and CAG (1, 2), several studies have reported that a considerable number of patients with *H. pylori* infection also expressed autoantibodies against H<sup>+</sup>/K<sup>+</sup>-ATPase (5–8). The presence of these autoantibodies in *H. pylori* infection was also significantly associated with higher fasting serum gastrin levels, a lower pepsinogen I to II ratio, and reduced secretion of gastric acid (8–10). In addition, pernicious anemia, which was earlier

considered as an exclusive complication of autoimmune gastritis (11), was also shown to be accompanied by *H. pylori* infection (12–14). On the basis of these histologic and clinical similarities, the hypothesis has been raised that classic autoimmune gastritis may be triggered by *H. pylori* infection (15, 16). However, pertinent evidence reported to date was primarily based on relatively small studies from the clinical setting. As a substantial proportion of CAGs are asymptomatic (17), and autoimmune gastritis is often an incidental diagnosis (18), large population-based studies are needed for a more comprehensive epidemiologic assessment. We therefore assessed the association of CAG with APCA positivity in a large population-based study, paying particular attention to the possible role of *H. pylori* infection.

## Materials and Methods

### Study population

The analyses are based on the baseline data of the ESTHER study (Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten Therapie chronischer ERkrankungen in der älteren Bevölkerung), a large population-based cohort study conducted among older adults in Saarland, Germany. Details of the study design have been reported elsewhere (19, 20). Briefly, 9,949 participants ages 50 to 74 years (mean age, 62 years) were recruited by their general practitioner during a general health check-up between July 2000 and December

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2002. Written informed consent was obtained from all participants. The study was approved by the ethics committees of the medical faculty of the University of Heidelberg and of the medical board of the State of Saarland, Germany.

### Data collection

**Questionnaire.** A standardized self-administrated questionnaire was completed by each participant, collecting information on sociodemographic characteristics, lifestyle factors, medical history, health status, and family history of major diseases.

**Laboratory analyses.** Serum samples were obtained from participants at the day of the health check-up, mailed to a central laboratory, and stored at  $-80^{\circ}\text{C}$  until laboratory analyses. Serum concentrations of pepsinogen I and II were measured by ELISA (Biohit). Immunoglobulin G (IgG) antibodies against *H. pylori* in general and the cytotoxin-associated gene A protein (CagA) were determined by ELISAs (*Helicobacter pylori* ELISA (Screen) and *Helicobacter pylori* p120 (CagA) ELISA, ravo Diagnostika). Classification of infection status was made according to the manufacturer's instructions, and borderline results were treated as negative. The sensitivity and specificity of the *H. pylori* serologic test was 96% and 74%, respectively, when compared with results of the  $^{13}\text{C}$ -urea breath test in a previous validation study conducted in 205 adult blood donors aged 40 to 68 years (19). APCAs against H+/K+-ATPase antigen were analyzed by ELISA (Euroimmun). APCA concentration was measured as optical density by plate-reader Anthos Reader 2010 (Mikrosysteme GmbH) and calculated according to point-to-point calibration curve. Serum dilution of 1:10 (serum:buffer) was used for initial measurement. Samples with values above the highest calibrator were diluted further until their value was within the range of calibration curve. The dilution factor was then applied to calculate APCA concentration. Test results were interpreted according to the manufacturer's instructions. All serologic examinations were carried out in a blinded fashion in the same laboratory.

### Statistical analysis

Of the 9,949 participants recruited in the ESTHER study, 7 with a previous diagnosis of gastric cancer and 258 without APCA concentrations (due to technical reasons unrelated to characteristics of the study population) were excluded from statistical analyses. The remaining 9,684 participants were characterized with respect to sociodemographic characteristics, lifestyle factors, family and own medical history, *H. pylori* infection, and CAG. The presence of CAG cases was determined by the following serology-based definition which has been commonly used in previous studies (21): pepsinogen I  $<70$  ng/mL and pepsinogen I/II  $<3$ .

The prevalence of APCA was examined according to age, sex, and *H. pylori* serostatus. Then, ORs and corresponding 95% confidence intervals (CI) for the association of APCA prevalence with CAG (overall and stratified by

*H. pylori* status, the latter further stratified according to CagA status) were estimated by logistic regression models, additionally controlling for age (years), sex, educational level (low/intermediate/high), smoking status (former smoker/current smoker/never smoker), alcohol consumption (g/week), and family history of gastric cancer (yes/no). A sensitivity analysis was conducted by excluding subjects who reported having had a history of *H. pylori* infection ( $n = 377$ ), duodenal ulcer ( $n = 929$ ), or both ( $n = 270$ ), as these participants would most likely have had *H. pylori* eradication therapy. Finally, we assessed the association of APCA positivity with various levels of severity of CAG which were defined according to quintiles of pepsinogen I level (20), with the lowest quintile indicating the most severe form of CAG. Again, these analyses were stratified according to *H. pylori* infection. Moreover, the analyses were repeated after excluding subjects who were *H. pylori* negative but CagA positive, as this constellation might be an indicator of past infection with *H. pylori* (22).

All analyses were conducted using the statistical software package SAS 9.2 (SAS Institute), and 2-sided *P* values of less than 0.05 were considered statistically significant.

### Results

Table 1 shows the characteristics of the study population. It included more women (54.6%) than men and the mean age was 62 years. Three quarters of the study population had less than 10 years of school education, and half of the participants had ever smoked. Approximately 6% of the subjects had a family history of gastric cancer. More than half of the participants presented serologic evidence of current or previous *H. pylori* infection (seropositive for either *H. pylori* in general or CagA antibodies). The serology-based prevalence of CAG in the study population was 5.4%.

Overall, approximately 20% of study participants have shown elevated levels of APCAs, with little variation by sex ( $P = 0.19$ ; Table 2). Overall, APCA seroprevalence slightly increased with age ( $P_{\text{trend}} = 0.002$ ), a trend that was though observed in men only ( $P_{\text{trend}} = 0.0003$ ). APCA was slightly more prevalent among *H. pylori* infected subjects than among those without *H. pylori* infection (20.7% versus 18.4%,  $P = 0.006$ ), and this difference in prevalence was due to a higher prevalence in participants with CagA-negative infection. Furthermore, the increase of APCA prevalence with age was confined to *H. pylori*-negative subjects ( $P_{\text{trend}} = 0.002$ ), but not observed among *H. pylori*-positive subjects.

Table 3 shows the associations between APCA prevalence and CAG derived from logistic regression. Overall, APCA prevalence was associated with an almost 4-fold increased risk of CAG (46.2% versus 18.0%, adjusted OR = 3.8; 95% CI: 3.1–4.7). Controlling for potential confounders as well as inclusion of *H. pylori* infection in the multiple regression model both had very little impact on the estimated association. However, a significant interaction between APCA status and *H. pylori* infection was detected

**Table 1.** Characteristics of the study population (n = 9,684)

Characteristics	N (%)
Sex	
Male	4,392 (45.4)
Female	5,292 (54.6)
Age (years)	
50–54	1,638 (16.9)
55–59	1,646 (17.0)
60–64	2,645 (27.3)
65–69	2,229 (23.0)
70–74	1,526 (15.8)
School educational <sup>a</sup>	
Low (≤9 years)	7,056 (74.8)
Intermediate (10–11 years)	1,331 (14.1)
High (12 years)	1,050 (11.1)
Smoking status <sup>b</sup>	
Never smoker	4,703 (50.0)
Former smoker	3,109 (33.0)
Current smoker	1,602 (17.0)
Alcohol consumption (g/day) <sup>c</sup>	
Abstainer	2,852 (32.6)
Low (women 0–19.99 g/day; men 0–39.99 g/day)	5,291 (60.5)
High (women ≥ 20 g/day; men ≥ 40 g/day)	602 (6.9)
Family history of gastric cancer <sup>d</sup>	
No	8,981 (94.2)
Yes	558 (5.8)
Helicobacter pylori infection <sup>e</sup>	
<i>H. pylori</i> –/CagA–	4,544 (47.3)
<i>H. pylori</i> –/CagA+	142 (1.5)
<i>H. pylori</i> +/CagA–	2,346 (24.4)
<i>H. pylori</i> +/CagA+	2,568 (26.8)
Chronic atrophic gastritis <sup>f</sup>	
No	8,806 (94.6)
Yes	504 (5.4)

<sup>a</sup>Data missing for 247 subjects.

<sup>b</sup>Data missing for 270 subjects.

<sup>c</sup>Data missing for 939 subjects.

<sup>d</sup>Data missing for 145 subjects.

<sup>e</sup>Data missing for 84 subjects.

<sup>f</sup>Data missing for 374 subjects.

( $P < 0.0001$ ). After stratification by *H. pylori* status, a substantially stronger association between APCA positivity and CAG was observed among *H. pylori*-negative subjects (OR = 11.3; 95% CI, 7.5–17.1) than among *H. pylori*-positive subjects (OR = 2.6; 95% CI, 2.1–3.3). In addition, a stronger association was seen among those with CagA-negative *H. pylori* infection compared with those with CagA-positive infection. Sensitivity analyses after excluding subjects with likely past *H. pylori* eradication had shown very similar results. For example,

APCA prevalence were 19.2%, 20.2%, and 18.4% among the overall, *H. pylori*-positive and *H. pylori*-negative subjects, respectively, and ORs for the association between APCA prevalence and CAG were 3.9 (95% CI, 3.2–4.9), 2.8 (95% CI, 2.2–3.6), and 10.5 (95% CI, 6.7–16.7), respectively.

Table 4 shows the association of APCA positivity with various levels of severity of CAG. In the absence of *H. pylori* infection, the association with APCA strongly increased with increasing severity of CAG defined by PGI levels. This pattern persisted even after excluding subjects who were *H. pylori* negative and CagA positive (data not shown). A much less pronounced dose-response pattern was seen among *H. pylori*-positive subjects.

### Discussion

In this large population-based study among older adults, we found APCA seropositivity to be strongly associated with CAG. While the association increased with the increasing level of disease severity in both *H. pylori*-negative and *H. pylori*-positive participants, the strength of the association and the dose-response pattern were much more pronounced in the former than in the latter group. Taken together, these results suggest that APCA may play a major role in the progression of CAG, independent from *H. pylori* infection.

Autoimmune gastritis is characterized by a chronic inflammatory infiltration in the gastric corpus mucosa as a result of autoimmune destruction mediated by APCAs (16), which is silent initially and becomes clinically manifest by the development of pernicious anemia (11) or is incidentally diagnosed due to other disorders (18). Most previous studies investigating the relation of CAG with autoimmune response and *H. pylori* infection were based on clinically selected populations and may therefore not have included the majority of asymptomatic CAG cases. To our knowledge, this is by far the largest population-based study that has systematically investigated the etiology of CAG, paying attention to the role of APCA and *H. pylori* infection simultaneously. In opposition to the previous finding that APCA prevalence increased with age in *H. pylori*-infected subjects (23), the age-dependence of APCA prevalence was confined to subjects without *H. pylori* infection in our study. A study conducted among patients with gastric diseases reported that the correlation between APCA levels and the extent of gastric atrophy (measured by pepsinogen I/II ratio) was limited to the *H. pylori*-positive group (24). In our large population-based study, the association of APCA and CAG increased more strongly with atrophic severity in *H. pylori*-negative than *H. pylori*-positive subjects.

Previous studies have reported on several sporadic CAG cases who were APCA positive but without any evidence of *H. pylori* infection. For example, APCA appeared during 32 years of follow-up in a subject who was *H. pylori* negative at both baseline and final examination (25), and studies conducted in childhood populations failed to detect *H. pylori* infection for some children

**Table 2.** Antiparietal cell antibodies seroprevalence in the study population

Group	Overall N (%)	Females N (%)	Males N (%)	<i>H. pylori</i> + N (%)	<i>H. pylori</i> – N (%)	<i>H. pylori</i> + CagA+ N (%)	<i>H. pylori</i> + CagA – N (%)
Overall	1,889 (19.5)	1,007 (19.0)	882 (20.1)	1,016 (20.7)	864 (18.4)	486 (18.9)	527 (22.5)
50–54 years	279 (17.0)	163 (17.1)	116 (16.2)	137 (18.9)	141 (15.6)	70 (18.6)	67 (19.2)
55–59 years	302 (18.4)	170 (18.8)	132 (17.8)	149 (20.6)	153 (16.8)	72 (19.7)	77 (21.6)
60–64 years	549 (20.8)	288 (20.2)	261 (21.4)	291 (21.4)	253 (20.0)	143 (20.2)	147 (22.7)
65–69 years	433 (19.4)	222 (18.4)	211 (20.7)	253 (20.8)	177 (17.8)	117 (17.9)	135 (24.0)
70–74 years	326 (21.4)	164 (19.6)	162 (23.5)	186 (20.7)	140 (22.5)	84 (18.1)	101 (23.4)
P <sub>trend</sub>	0.002	0.56	0.0003	0.45	0.002	0.56	0.10

with APCA (15, 26, 27). In addition, APCA and *H. pylori* infection have been suggested to be associated with different HLA-DQ haplotypes in patients with type I diabetes (28). In another study, APCA antibodies did not decrease after cure of *H. pylori* infection over 1 year for a portion of patients (29). In line with our results, these findings suggest that APCA-mediated autoimmune gastritis may frequently be induced by other unknown factors or diseases that are unrelated to *H. pylori* infection.

Of note, it has been suggested that histologically defined early stages of autoimmune gastritis can be successfully treated by *H. pylori* eradication (30–32), which supported the hypothesis that infection with *H. pylori* may trigger APCA-mediated autoimmune response in a subset of infected patients. However, conflicting results have also been reported (24, 29). Simultaneous occurrence of *H. pylori* infection and autoimmune reaction observed in previous investigations (5–8) or our study population cannot be interpreted to support a causal relationship between bacterial infection and autoimmune response. Because of the cross-

sectional study design with simultaneous ascertainment of infection, autoimmune response and CAG, temporal relationships between occurrence of bacterial infection, autoimmune response and development of CAG as well as potential disease-related loss of *H. pylori* infection could not be observed. Longitudinal studies with repeated measurement of these parameters during life course would be needed for definitive clarification of the interdependencies.

*Helicobacter pylori* strains that express the *cagA* gene located at the end of the *cag* pathogenicity island have been identified to cause enhanced inflammatory response, elevated serum gastrin levels, and increased risk for gastric malignancies (33). Only 2 previous studies have examined the role of this virulence factor in relation to APCA. One study reported that the presence of APCA was not associated with CagA status based on 49 patients (34), whereas in the other study, APCA was detected in 10 of 19 (52.6%) CagA-positive and 19 of 23 (82.6%) CagA-negative subjects ( $P < 0.05$ ) (35). Our large study also found that APCA was more prevalent in CagA-

**Table 3.** Association between APCA seroprevalence and CAG according to *H. pylori* serostatus

Group	APCA serostatus	N	CAG		OR (95% CI)	
			N	%	Model 1 <sup>a</sup>	Model 2
Overall	negative	7,490	271	3.6	1.00	1.00
	positive	1,820	233	12.8	3.9 (3.1–4.7)	3.8 (3.1–4.7) <sup>b</sup> 3.8 (3.1–4.6) <sup>c</sup>
<i>H. pylori</i> –	negative	3,709	34	0.9	1.00	1.00
	positive	834	86	10.3	11.2 (7.4–16.8)	11.3 (7.5–17.1) <sup>b</sup>
<i>H. pylori</i> +	negative	3,781	237	6.3	1.00	1.00
	positive	986	147	14.9	2.6 (2.1–3.3)	2.6 (2.1–3.3) <sup>b</sup>
<i>H. pylori</i> +/CagA–	negative	1,755	46	2.6	1.00	1.00
	positive	508	66	13.0	5.5 (3.7–8.3)	5.7 (3.8–8.6) <sup>b</sup>
<i>H. pylori</i> +/CagA+	negative	2,017	189	9.4	1.00	1.00
	positive	474	81	17.1	2.0 (1.5–2.7)	2.0 (1.5–2.7) <sup>b</sup>

<sup>a</sup>OR without adjustment.  
<sup>b</sup>OR adjusted for age, sex, family history of gastric cancer, educational level, smoking status, alcohol consumption.  
<sup>c</sup>OR adjusted for *H. pylori* infection.

**Table 4.** Association of APCA prevalence with CAG according to CAG severity

Group	OR (95% CI) for the association of APCA prevalence with CAG by CAG severity <sup>a</sup>				
	PG I Quintile 5 (35.01–69.99 ng/mL)	PG I Quintile 4 (22.19–35.00 ng/mL)	PG I Quintile 3 (14.55–22.18 ng/mL)	PG I Quintile 2 (8.58–14.54 ng/mL)	PG I Quintile 1 (<8.58 ng/mL)
Overall	1.9 (1.2–2.9)	3.0 (1.9–4.5)	2.6 (1.7–4.1)	5.1 (3.4–7.6)	10.9 (6.9–17.1)
<i>H. pylori</i> –	1.5 (0.3–7.1)	4.1 (1.3–13.7)	7.7 (2.9–20.4)	19.0 (7.7–47.4)	23.1 (10.7–49.9)
<i>H. pylori</i> +	1.8 (1.1–2.9)	2.6 (1.7–4.1)	2.0 (1.2–3.2)	3.0 (1.8–4.9)	6.2 (3.4–11.1)

<sup>a</sup>OR adjusted for age, sex, family history of gastric cancer, educational level, smoking status, alcohol consumption.

negative infection, and the association between APCA prevalence and CAG was much stronger among subjects with CagA-negative infection compared with subjects with CagA-positive infection. This observation gives further support to the suggestion that APCA presence is not primarily triggered by *H. pylori* virulence, and that a substantial proportion of *H. pylori* infections, in particular CagA positive infections, are likely to lead to CAG through pathways other than autoimmune response. On the other hand, another member of the *cag* pathogenicity island, CagE, has been shown to induce parietal cell apoptosis *in vitro* (36). Additional virulence factors of this infectious agent relevant to induction of autoimmune response warrant further investigation.

In the interpretation of our study, additional limitations have to be considered. CAG was not confirmed by histology, as it is impractical to implement gastroscopy in a large-scale epidemiologic study outside special-risk groups. Although gastroscopy-based histologic diagnosis is often considered as the gold standard for determining atrophic gastritis, it also suffers from specific limitations, such as sampling errors (37), and inter- and intraobserver variation (38). Advantages of measurements of serum pepsinogen levels are the high degree of standardization and the fact that they reflect an integrative quantitative measure of the gastric mucosal function. Serologic measurement of *H. pylori* infection is likewise less than perfect and may have led to some alteration of differences between infected and non-infected participants by misclassification of infection status.

In summary, despite its limitations, our large population-based study substantially expands existing evidence on the interrelationship between *H. pylori* infection and APCA-mediated autoimmune response in the development of CAG. Our results suggest that *H. pylori* infection and APCA-mediated autoimmune response might, for the most part, be independent, distinct pathways, rather than causally related pathways leading to CAG. Assessment of APCA might be a useful complement to established markers (such as pepsinogens and *H. pylori* antibodies) in screening for CAG.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

**Authors' Contributions**

**Conception and design:** M. Weck, D. Rothenbacher, H. Brenner  
**Development of methodology:** M. Weck  
**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** M. Weck, D. Rothenbacher, H. Brenner  
**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** Y. Zhang, H. Brenner  
**Writing, review, and/or revision of the manuscript:** Y. Zhang, B. Schöttker, D. Rothenbacher, H. Brenner  
**Study supervision:** H. Brenner

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