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A Combination of Fasting Serum Gastrin Concentration, Pepsinogen 1/2 Ratio and *Helicobacter pylori* IgG Antibody Serotype Accurately Predicts Gastric Mucosal Preneoplasia in a Large European Cohort

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Introduction *H. pylori* infected subjects who develop corpus-predominant gastritis have an increased risk of developing gastric cancer. Gastric adenocarcinoma develops via a well-defined series of pathological changes namely multi-focal atrophy, intestinal metaplasia, dysplasia and finally cancer. In high-risk populations, serological biomarkers for screening and surveillance have been well validated. In European populations with a lower prevalence of gastric cancer however, circulating biomarkers have only been evaluated in small series and contradictory results have been described. Methods We recruited 1400 symptomatic adults (57.5% female, mean age 58 years, 98.4% Caucasian) after referral to our hospital in North-West England for diagnostic upper gastrointestinal endoscopy. Blood and gastric biopsy specimens were obtained. *H. pylori* status was determined by histology and serum IgG antibody ELISA. Fasting serum gastrin concentrations were measured by radioimmunoassay using a C-terminal specific antibody and serum pepsinogen (PG) 1 and 2 concentrations by ELISA. A single, expert gastrointestinal histopathologist examined antral and corpus biopsy specimens and produced standardized reports. Results *H. pylori* serology was positive in 577 (41.2%) patients. Of these 294 (51.3%) also had histological evidence of current *H. pylori* infection. Preneoplastic mucosal lesions were reported in 338 (24.1%). The prevalence of *H. pylori* antibodies in subjects with preneoplasia (68.3%) was significantly greater than in those without (36.6%) ($p<0.0001$). Subjects with preneoplasia also exhibited significantly higher fasting serum gastrin concentrations (mean=148.4pM) than normal controls who were *H. pylori* negative and did not take proton pump inhibitors (mean=39.7pM) ($p< 0.0001$). There was no significant difference between serum PG1 concentration in normal controls (98.9µg/l) and patients with preneoplasia (115.0µg/l). Serum PG2 concentration however differed significantly in preneoplasia patients (17.2µg/l) compared with controls (9.23µg/l), as did PG1/2 ratio (7.20 versus 11.54) ($p<0.0001$). PG1/2 ratio performed better as a diagnostic test for preneoplasia than either PG1 or PG2 concentration. With a cutoff of 8.8, we observed a sensitivity of 70.0% and a specificity of 79.1% with an area under the receiver-operating curve of 0.80. Combining PG1/2 ratio, fasting serum gastrin concentration and *H. pylori* serology improved the diagnostic accuracy. The combined test yielded a sensitivity of 90.0% and a specificity of 74.4% with positive and negative predictive values of 52.1% and 96.0% respectively. Conclusion The combined test is an accurate predictor of the presence of gastric mucosal preneoplasia in a European cohort. Clinical applications including screening of symptomatic patients or surveillance of at-risk groups and merit further investigation.