Establish Screening Model for *H. pylori*-infected Subjects with High Risk of Gastric Cancer and Post-*H. pylori* Eradication Surveillance

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Background: Helicobacter pylori (H. pylori)-infected non-ulcer dyspepsia (NUD) subjects are at risk of gastric cancer. A marker earlier than intestinal metaplasia is in need to select subjects for early H. pylori eradication to prevent gastric cancer. A novel marker, corpus-predominant gastritis index (CGI), correlates with spasmolyic polypeptide-expressing metaplasia (SPEM) in H. pylori-infected gastric cancer relatives. A large-scale longitudinal study is necessary to validate whether CGI or SPEM is more prevalent in NUD and is reversible by H. pylori eradication. **Aims:** This study validated whether CGI is more prevalent in H. pylori-infected NUD subjects than in duodenal ulcer (DU) controls and whether CGI could be reversible after Helicobacter pylori eradication or is correlated to non-invasive biomarkers. **Methods:** In this longitudinal cohort study, 573 Helicobacter pylori-infected subjects were enrolled, including 349 NUD and 224 DU. Gastric specimens were provided to assess CGI, spasmolyic polypeptide-expressing metaplasia (SPEM), and Operative Link on Gastric Intestinal Metaplasia assessment (OLGIM). Serum pepsinogen I and II levels were assessed using enzyme-linked immunosorbent assay. CGI subjected were followed up at least one year after Helicobacter pylori eradication. In vitro, TFF2 and RUNX3 protein expression of GES1 cells co-cultivated with H. pylori strains were compared between different H. pylori strains. H. pylori strains included the Hp1033 cancer strain, the standard strain 26695 (strong CagA phosphorylation activity), J99 and the Hp1033 DK replacement strain (weak CagA phosphorylation activity), and the Hp1033 cagA mutant strain (no CagA phosphorylation activity). **Results:** NUD subjects had higher prevalence rates of CGI (47.0% vs. 29.9%, $P < 0.001$) and OLGIM stage II-IV (30.1% vs. 19.2%, $P = 0.004$) than controls. CGI was highly prevalent in NUD subjects after the age of 40, which was 10 years earlier than atrophic gastritis and intestinal metaplasia. NUD subjects with CGI had higher risk of SPEM (OR 2.86, $P < 0.001$) and lower serum pepsinogen I/II ratios ($P < 0.001$) than those without CGI. Serum pepsinogen I/II ratios < 9 could predict CGI modestly (AUROC 0.69, 95% CI 0.63-0.74). CGI, not SPEM, was regressed after eradication ($P < 0.001$). *In vitro*, TFF2 protein was up-regulated significantly in GES-1 cells co-cultivated with Hp1033 and 26695 (both $P = 0.037$) but the up-regulation was abolished in cells co-cultivated with the Hp1033 cagA mutant strain (Hp1033 vs. Hp1033 cagA mutant strain, $P = 0.05$). RUNX3 protein was down-regulated significantly in GES-1 cells co-cultivated with Hp1033 ($P = 0.01$) and 26695 ($P = 0.007$) but the down-regulation was abolished in cells co-cultivated with the Hp1033 cagA mutant strain (Hp1033 vs. Hp1033 cagA mutant strain, $P = 0.025$). **Conclusions:** CGI was more prevalent in NUD subjects than in duodenal ulcer controls. NUD subjects with CGI had increased risk of SPEM as compared to those without CGI. Serum pepsinogen I/II ratios predicted CGI in NUD at a modest level of accuracy. CGI could be regressed in NUD subjects after H. pylori eradication. CagA may play a role to up-regulate TFF2 and down-regulate RUNX3 expression in gastric epithelial cells.