Research Paper

Clinical significance of serum markers reflecting gastric function and \textit{H. pylori} infection in colorectal cancer

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Abstract

\textbf{Purpose:} The study was conducted to investigate the relationship of serum pepsinogens PGI, PGII, gastrin-17, and Hp-IgG with colorectal cancer (CRC), aiming to explore the clinical significance of serum markers reflecting gastric function and \textit{H. pylori} infection in CRC.

\textbf{Methods:} A total of 569 CRC cases and 569 age and sex-matched controls were enrolled in this study between June 2012 and April 2016 from The First Hospital of China Medical University. The serum markers reflecting gastric function and \textit{H. pylori} infection were detected using ELISA, including PGI, PGII, PGI/II ratio, G-17 and Hp-IgG. Information of clinicopathological parameters and tumor biomarkers was collected from the medical records of inpatients, including CEA, CA199, CA125, CA153 and AFP.

\textbf{Results:} Serum PGII, G-17 levels and Hp-IgG were increased in CRC, while PGI and PGI/II ratio appeared no significant difference between CRC and controls. In subgroup analysis, PGII was more significant in males ($P=0.014$). Hp-IgG was demonstrated higher in age<60y ($P=0.001$). With respect to the association with serum tumor biomarkers, G-17 level was associated with the rise of CA125 ($P=0.005$, OR (95%CI): 4.89 (1.90-12.57)), Hp-IgG increasing was associated with the rise of CA125 ($P=0.024$, OR (95%CI): 4.10 (1.54-10.93)).

\textbf{Conclusions:} Serum PGII, G-17 and Hp-IgG were associated with CRC risk. The serum levels of G-17 and Hp-IgG were associated with the rise of CA125 in patients with CRC

Key words: Gastric function; Pepsinogens; Gastrin; \textit{H. pylori}; Colorectal cancer

Introduction

As an organ in upper digestive tract, the stomach is responsible for digestion and decomposition of food; while the colorectum, as an organ in lower digestive tract, mainly absorb water and electrolytes, and store fecal material until it is evacuated. They have similarities in anatomical structure and organizational level. Despite their own characteristics, the stomach and colorectum are interacted with each other.

Although the incidence of gastric cancer (GC) and colorectal cancer (CRC) has different trends in the Western population: a marked decrease has been observed in GC during last decades in many countries, while a stable or increasing trend has been described for CRC [1], there have been epidemiological studies showing that the upper and lower gastrointestinal organs (stomach, colon and rectum) have many similarities in the genesis and development of cancer. For example, changing diet, activity patterns and smoking are involved in their carcinogenesis [1]. Moreover, they have some tumor markers in common [2, 3], such as CEA, CA199, CDX2, etc. Therefore, it is reasonable to infer that some similar functional factors may participate in the development of GC and CRC. As we know, GC can be divided into intestinal and diffuse types.
histologically. Intestinal-type GC (IGC) is based on the intestinal metaplasia of gastric mucosa. Newbold [4] suggested common histogenesis between IGC and CRC by demonstrating that similar clusters of undifferentiated proliferating columnar cells occurred in the mucosal surfaces associated with intestinal metaplasia in stomach and adenomatous polyps in colorectum. It has been paid great attention to whether IGC and CRC have function alteration in common [5-7].

Pepsinogen (PG) and gastrin (G-17) are secreted by gastric mucosa and a fraction of them are released into blood. Detection of the secreted protein (PGs, G-17) levels in serum can indirectly evaluate the function status of stomach. H. pylori can cause immune response and induce drug resistance after infection in human body. It would improve the knowledge of H. pylori infection status of stomach to examine its antibody (HpAb) in serum. Previously, a lot of researches have suggested that the serum markers reflecting gastric function (PGs, G-17) and H. pylori infection (Hp-IgG) play important roles in GC screening as serological biopsy, especially for IGC and gastric precancerous diseases [8-10]. However, it remains unclear whether the function of upper digestive tract organs may affect lower tract organs and whether GC-related risk markers also indicate an increased risk of CRC.

Here, we conducted a hospital-based case-control study to clarify the association of serum markers reflecting gastric function and H. pylori infection with CRC, including pepsinogen (PGI, PGII, PGI/II ratio), G-17 and Hp-IgG, aiming to explore the clinical significance of these serum markers in CRC.

Materials and Methods

Study population

The present study was approved by the Human Ethics Review Committee of The First Hospital of China Medical University (Shenyang, China). Informed consent was obtained from all participants. The cases (n=569) were diagnosed with CRC after surgery in the Anorectal Surgery Department of The First Hospital of China Medical University between June 2012 and April 2016. Controls (n=569) were randomly selected from the cancer-free individuals seeking for physical examination in the Medical Examination Department in The First Hospital of China Medical University during the same period. The controls were frequency-matched to the cases based on gender and age (±5 years).

A total of 625 CRC cases were recruited in our study initially. According to the inclusion and exclusion criteria, 569 cases were finally enrolled after removal of the individuals that refused to get involved. Inclusion criteria: i) CRC cases were diagnosed by postoperative pathology, combined with imaging examination for staging, all cases were diagnosed as adenocarcinoma; ii) No preoperative chemotherapy, radiation therapy and any anti-tumor treatment; iii) No malignant tumors of other systems and no distant metastasis; iv) No history of upper gastrointestinal diseases; v) Information in medical records was complete. Exclusion criteria: i) Previous surgery, radiotherapy, chemotherapy; ii) Severe comorbidities, including hepatic, renal, cardiopulmonary, and hematologic diseases; iii) Preoperative distant metastasis or primary tumor of other organs; iv) History of basic diseases in the digestive tract; v) Non-radical surgery; vi) Incomplete information in medical records.

A total of 2004 controls were recruited in our study initially. According to the inclusion and exclusion criteria, 569 controls were finally enrolled after removal of the individuals that refused to get involved. Inclusion criteria: i) No abnormality in regular imaging examination (e.g. lung CT, abdominal CT); ii) No abnormality in routine test (e.g. blood routine, liver and kidney function, tumor biomarkers); iii) No malignancy in any system; iv) No history of upper gastrointestinal diseases; v) Information in medical records was complete. Exclusion criteria: i) Abnormality in imaging examination or tests; ii) History of malignancy in any system; iii) History of severe diseases, including hepatic, renal, cardiopulmonary and hematologic diseases; iv) History of basic diseases in the digestive tract; v) Information in medical records was incomplete.

Serological detection

Fasting venous blood samples (5mL) were collected from each CRC case for detection of serum markers reflecting gastric function and H. pylori infection before surgery (average 7 days) after admission. Fasting venous blood samples (5mL) were also collected from controls when they visited Medical Examination Department.

Samples were centrifuged immediately at 3,500g for 10 minutes, and serum aliquot was immediately frozen and stored at –80°C until analysis. Serum PGI, PGII, G-17 and Hp-IgG were detected using enzyme-linked immunosorbent assays (BIOHIT Plc, Helsinki, Finland) according to the manufacturer's protocols. Samples that yielded implausible values were re-tested. Duplicate negative and positive controls were included in each 96-well plate. The mean intra-assay coefficients of variation (CV) were 11% for PGI, 12% for PGII, 15% for gastrin-17 and 11% for Hp-IgG. The test items and reference ranges were
Clinical pathological information collection

Clinical pathological data collection was performed according to the AJCC TNM system (7th edition, 2010)[13] and parameters such as histopathological grade, gross type, depth of infiltration, lymph node metastasis, TNM stage, growth mode, vascular carcinoma embolus, perineural invasion and ENTD (extranodal tumor deposits) were taken notes.

Table 1. Baseline characteristics of the study participants

<table>
<thead>
<tr>
<th>Indexes</th>
<th>CRC</th>
<th>Controls</th>
<th>CRC vs Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, mean ± SD)</td>
<td>62.0±11.0</td>
<td>60.8±9.6</td>
<td>0.055</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>331(58.2)</td>
<td>304(53.4)</td>
<td>0.107</td>
</tr>
<tr>
<td>Female</td>
<td>238(41.8)</td>
<td>265(46.6)</td>
<td></td>
</tr>
<tr>
<td>PGI (ug/L)</td>
<td>9.9(7.8~132.3)</td>
<td>8.2(65.5~100.4)</td>
<td></td>
</tr>
<tr>
<td>PGII (ug/L)</td>
<td>7.2(4.6~15.6)</td>
<td>7.6(6.0~11.0)</td>
<td></td>
</tr>
<tr>
<td>G-17 (pmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hp-IgG</td>
<td>265(46.6)</td>
<td>265(36.0)</td>
<td></td>
</tr>
</tbody>
</table>

a: Data are expressed as frequency and percentages.
b: Data are expressed as median (25th to 75th percentiles).

Statistical analysis

Continuous variables were presented as median (25th to 75th percentiles). Categorical variables were compared between groups using Chi-square test and multiple logistic regression. Regardless of unavailable information of other CRC risk factors, the odds ratios (ORs) with 95% confidence intervals (95%CIs) were calculated to evaluate the association adjusted by age and sex. Additionally, heterogeneity tests were conducted for stratification analysis using the Episheet (Spreadsheets for the Analysis of Epidemiologic Data, written by Ken Rothman, Version of October 4, 2012). The Bonferroni correction was adopted to adjust P values for multiple comparisons. The remaining statistical analyses were performed using SPSS 22.0 software. P<0.05 (two-sided) was considered to be statistically significant.

Results

Baseline characteristics of the study participants

The CRC and control groups were matched based on age (P=0.055) and gender (P=0.107). The baseline characteristics of the study participants were presented in Table 1.

Association of serum markers reflecting gastric function and H. pylori infection with CRC risk

Overall analysis for the levels of serum markers reflecting gastric function and H. pylori infection between CRC cases and controls was presented in Table 2. Compared with the controls, serum PGII, G-17 and Hp-IgG was higher in CRC cases (P=0.006, P<0.001, P=0.001 respectively). No significant difference in PGI and PGI/II ratio was found between CRC cases and controls.

Table 2. Association of serum markers reflecting gastric function and H. pylori infection with CRC risk

<table>
<thead>
<tr>
<th>Indexes</th>
<th>CRC</th>
<th>Controls</th>
<th>CRC vs Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGI/PGII</td>
<td>106/463(18.63)</td>
<td>133/436(23.37)</td>
<td>0.096</td>
</tr>
<tr>
<td>PGII/GP</td>
<td>339/230(59.58)</td>
<td>278/291(48.86)</td>
<td>0.006</td>
</tr>
<tr>
<td>G-17/GP</td>
<td>134/435(20.65)</td>
<td>127/442(22.02)</td>
<td>0.650</td>
</tr>
<tr>
<td>H.p/IgG</td>
<td>197/372(34.62)</td>
<td>124/445(21.79)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

a: Percentages of positivity.
b: Adjusted by age and sex.
c: Adjusted by age, sex and Hp-IgG.

To identify other factors that may affect the gastric function indicators, we also analyzed the correlation among the gastric function markers and Hp-IgG, and found there are some correlation exist, we list the results in (Table S1). In addition, the association analyses were also performed adjusted by all the gastric function indicators other than age and sex unless one of them was regarded as the analyzed item. Similar results could be observed. Serum PGII/II, G-17 and Hp-IgG were higher in CRC cases than the controls (Table S2).

Stratified analysis for the levels of serum markers reflecting gastric function and H. pylori infection between CRC cases and controls was presented in Table 3. PGII was more significant in the subgroup of males (P=0.014, P_heterogeneity=0.362). Hp-IgG demonstrated a higher association with CRC in the subgroup of age<60y (P=0.001, P_heterogeneity=0.094). G-17 was more significant in the Hp-IgG negative subgroup (P<0.001, P_heterogeneity<0.001). PGII and PGI/II ratio were
positively associated with CRC in the Hp-IgG negative subgroup and inversely associated in the Hp-IgG positive subgroup ($P_{\text{heterogeneity}} < 0.001$ and $< 0.001$, respectively).

**Association of serum markers reflecting gastric function and *H. pylori* infection with tumor biomarkers**

The relationship of PGI, PGII, PGI/II ratio, G-17 and Hp-IgG levels with serum tumor biomarkers in CRC cases was presented in Table 4. All the cases with available information of tumor biomarkers in medical records were analyzed (CEA 429 cases, AFP 426 cases, CA125 428 cases, CA153 424 cases and CA199 428 cases). Significant positive association was found between G-17 and CA125 ($P = 0.005$), as well as Hp-IgG and CA125 ($P = 0.024$). No association was observed in the serum levels of PGI, PGII and PGI/II ratio with tumor biomarkers.

### Table 3. Association of serum markers reflecting gastric function and *H. pylori* infection with CRC risk in subgroups

<table>
<thead>
<tr>
<th>Age</th>
<th>PGI +/PGI-</th>
<th>OR (95% CI)</th>
<th>PGI +/PGII-</th>
<th>OR (95% CI)</th>
<th>PGI II+/PGII-</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60</td>
<td>223/107</td>
<td>1.55 (1.13-2.12)</td>
<td>224/107</td>
<td>1.55 (1.13-2.12)</td>
<td>230/108</td>
<td>1.63 (1.22-2.16)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>216/109</td>
<td>1.63 (1.22-2.16)</td>
<td>217/109</td>
<td>1.63 (1.22-2.16)</td>
<td>222/110</td>
<td>1.63 (1.22-2.16)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th>PGI +/PGI-</th>
<th>OR (95% CI)</th>
<th>PGI +/PGII-</th>
<th>OR (95% CI)</th>
<th>PGI II+/PGII-</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>205/106</td>
<td>1.63 (1.18-2.29)</td>
<td>206/106</td>
<td>1.63 (1.18-2.29)</td>
<td>211/107</td>
<td>1.63 (1.18-2.29)</td>
</tr>
<tr>
<td>Female</td>
<td>216/109</td>
<td>1.63 (1.22-2.16)</td>
<td>217/109</td>
<td>1.63 (1.22-2.16)</td>
<td>222/110</td>
<td>1.63 (1.22-2.16)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hp-IgG</th>
<th>PGI +/PGI-</th>
<th>OR (95% CI)</th>
<th>PGI +/PGII-</th>
<th>OR (95% CI)</th>
<th>PGI II+/PGII-</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>216/106</td>
<td>1.63 (1.18-2.29)</td>
<td>217/106</td>
<td>1.63 (1.18-2.29)</td>
<td>222/110</td>
<td>1.63 (1.22-2.16)</td>
</tr>
<tr>
<td>-</td>
<td>205/106</td>
<td>1.63 (1.18-2.29)</td>
<td>206/106</td>
<td>1.63 (1.18-2.29)</td>
<td>211/107</td>
<td>1.63 (1.18-2.29)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>G-17+/G-17-</th>
<th>OR (95% CI)</th>
<th>HP-IgG+/HP-IgG-</th>
<th>OR (95% CI)</th>
<th>HP-IgG -/HP-IgG-</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60</td>
<td>154/176</td>
<td>1.34 (0.98-1.82)</td>
<td>155/176</td>
<td>1.34 (0.98-1.82)</td>
<td>156/176</td>
<td>1.34 (0.98-1.82)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>111/128</td>
<td>2.03 (1.39-2.96)</td>
<td>112/128</td>
<td>2.03 (1.39-2.96)</td>
<td>113/128</td>
<td>2.03 (1.39-2.96)</td>
</tr>
</tbody>
</table>

### Table 4. Association of serum markers reflecting gastric function and *H. pylori* infection with tumor biomarkers

<table>
<thead>
<tr>
<th>PGI</th>
<th>OR (95% CI)</th>
<th>PGI</th>
<th>OR (95% CI)</th>
<th>PGI</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA(N=429)</td>
<td>+ 36/153 19.05 (1.00-61.64)</td>
<td>- 46/194 19.17 (1.00-61.64)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFP(N=426)</td>
<td>+ 2/11 15.38 (0.60-66.14)</td>
<td>- 78/335 18.99 (0.60-66.14)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CA125(N=428)</td>
<td>+ 5/17 22.73 (1.57-55.45)</td>
<td>- 77/329 18.96 (1.57-55.45)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CA153(N=424)</td>
<td>+ 0/8 0 (0.00-75)</td>
<td>- 80/336 19.23 (0.00-75)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CA199(N=426)</td>
<td>+ 24/85 22.02 (1.23-72.21)</td>
<td>- 57/262 17.87 (1.23-72.21)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>G17</th>
<th>OR (95% CI)</th>
<th>HP-IgG</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA(N=429)</td>
<td>+ 6/127 32.80 (0.47-84.56)</td>
<td>- 88/152 36.67 (0.47-84.56)</td>
<td></td>
</tr>
<tr>
<td>AFP(N=426)</td>
<td>+ 4/9 30.77 (0.70-79.24)</td>
<td>- 145/268 35.11 (0.70-79.24)</td>
<td></td>
</tr>
<tr>
<td>CA125(N=428)</td>
<td>+ 15/7 68.18 (0.00-90.12)</td>
<td>- 135/271 33.21 (0.00-90.12)</td>
<td></td>
</tr>
<tr>
<td>CA153(N=424)</td>
<td>+ 5/5 62.50 (0.10-73.50)</td>
<td>- 142/274 34.13 (0.10-73.50)</td>
<td></td>
</tr>
<tr>
<td>CA199(N=426)</td>
<td>+ 32/77 29.36 (0.15-71.44)</td>
<td>- 117/202 36.68 (0.15-71.44)</td>
<td></td>
</tr>
</tbody>
</table>

a: Adjusted by age.
b: Adjusted by age and sex.
c: Adjusted by age, sex, and PGI.

http://www.jcancer.org
Association of serum markers reflecting gastric function and H. pylori infection with CRC clinicopathological parameters

The relation of gastric function indicators and Hp-IgG to CRC clinicopathological parameters was presented in Table S4. Totally, 556 CRC cases with complete clinicopathological parameters information were involved in the analysis. However, no significance was indicated between gastric function indicators, Hp-IgG and any of the CRC clinicopathological parameters assessed.

Discussion

To explore the clinical significance of serum markers reflecting gastric function and H. pylori infection in CRC, we investigated the association of serum PGI, PGII, G-17 and Hp-IgG with CRC risk, tumor biomarkers and CRC clinicopathological parameters, aiming to provide the basis for diagnosis and treatment of CRC by applying these functional indicators. As far as we concern, this is the first report on the clinical significance of all gastric function indicators together combined with CRC.

As important organs of the whole digestive tract, both stomach and colorectum have not only anatomical structural similarities, but also functional correlations. As we know, PGs are specific products in the terminal differentiation of gastric mucosa. They are of diagnostic value for atrophic gastritis and have some roles as risk markers and screening tools for GC [14]. In our study, the association of PGI, PGII and PGI/II ratio with CRC was explored. PGI is mainly secreted by chief cells in the fundic mucosa, and is generally applied to evaluate the function in different sites of gastric mucosa. A long term follow-up study[15] and a case-control study[16] reported no association between serum PGI level and CRC. In the present study, we found that the serum level of PGI did not indicate relations to CRC risk which is similar to previous results. PGII is secreted by pyloric glands and proximal duodenal mucosa. Previous studies suggested that the serum PG assay was more beneficial for the screening of IGC than for the diffuse-type GC, especially in the case of a high PG II level [17]. In the present study we found a higher level of PGII in CRC. Sushil Kumar et al [18] had reported that patients with IM had higher level of PG II than those without IM. Intestinal metaplasia might cause hypochlorhydria which hampers protein assimilation, increases some metabolites and unabsorbed nutrients, leads to bacterial overgrowth and colonic disorders, and thus affects the internal environment and intestinal function, being related to intestinal tumorigenesis [19, 20]. In view of these findings, it can be inferred that PGII may promote intestinal metaplasia, affect intestinal mucosa through similar mechanism and thus result in CRC initiation. PGI/II ratio is very valuable in predicting the development of atrophic gastritis [21] and GC [22]. Yanaoka, Oka et al. reported that PGI/II ratio was a reliable marker for intestinal-type GC [23]. Dinis-Ribeiro et al [24] found that PGI/II ratio would be significantly decreased with carcinogenesis (type II, type III IM or low-grade dysplasia). However, in the present study we found that the serum level of PGI/II ratio did not indicate relations to CRC risk. Up to now, no research has reported the correlation between PGI/II ratio and CRC risk. It is necessary to expand further studies to verify our initial results. In addition to the overall analysis, we did a subgroup analysis based on different ages and genders in our study. Only PGII was found more significant in the males. Many epidemiological investigations have shown that the prevalence and mortality of CRC are higher in men than in women. Such disparities can be attributed to gender-specific lifestyle and behavioral characteristics which can influence the effects of exposure to genotoxins. Our finding that the serum PGII levels were higher in male subjects than in female subjects is in agreement with some earlier studies, such as an study in health check-up population [25] and another one in different gastric diseases population [11]. These data suggested that in clinical applications, it could be preferable to set different reference values for males and females.

As a peptide hormone and trophic factor, gastrin has been suggested to play a growth-promoting role in gastrointestinal malignancy in addition to regulating gastric acid secretion [26]. Gastrin and its receptor were expressed in the gastric mucosa of patients with premalignant lesions of the lower gastrointestinal tract [27], and the gastrin system might also be able to promote colon carcinogenesis [28]. Although previous research had investigated on the relationship of gastrin with colorectal neoplasia [27], and the gastrin system might also be able to promote colon carcinogenesis [28]. Although previous research had investigated on the relationship of gastrin with colorectal neoplasia [27], and the gastrin system might also be able to promote colon carcinogenesis [28]. Although previous research had investigated on the relationship of gastrin with colorectal neoplasia [27], and the gastrin system might also be able to promote colon carcinogenesis [28]. Although previous research had investigated on the relationship of gastrin with colorectal neoplasia [27], and the gastrin system might also be able to promote colon carcinogenesis [28]. Although previous research had investigated on the relationship of gastrin with colorectal neoplasia [27], and the gastrin system might also be able to promote colon carcinogenesis [28]. Although previous research had investigated on the relationship of gastrin with colorectal neoplasia [27], and the gastrin system might also be able to promote colon carcinogenesis [28]. Although previous research had investigated on the relationship of gastrin with colorectal neoplasia [27], and the gastrin system might also be able to promote colon carcinogenesis [28]. Although previous research had investigated on the relationship of gastrin with colorectal neoplasia [27], and the gastrin system might also be able to promote colon carcinogenesis [28]. Although previous research had investigated on the relationship of gastrin with colorectal neoplasia [27], and the gastrin system might also be able to promote colon carcinogenesis [28]. Although previous research had investigated on the relationship of gastrin with colorectal neoplasia [27], and the gastrin system might also be able to promote colon carcinogenesis [28].
Moreover, colorectal carcinoma cells could aberrantly generate gastrin as well. Hence, gastrin may act as an autocrine/paracrine or endocrine factor in the initiation and progression of colorectal carcinoma [26].

Regarding the association between H. pylori infection and CRC risk, the results in different literature were inconsistent. Several meta-analyses [35-37] suggested increased CRC risk associated with H. pylori infection. However, some findings did not support a significant association between H. pylori infection and CRC [38-40]. In our study, the serum Hp-IgG was higher in CRC cases than in controls, especially in the subgroup of age<60y. A prospective cohort study found that H. pylori infection was associated with a 60–80% increase in CRC risk and this association was particularly strong with colon cancer diagnosed at <55 years of age [41]. It is well accepted that gastric adenocarcinoma, especially the intestinal-type, is based on a long-term precancerous course promoted by H. pylori [42]. Most CRC cases derive from adenomas, and H. pylori-related IM was identified as an independent risk factor for colorectal adenoma in Chinese older than 40y [43]. Therefore, H. pylori may act alone or have synergistic effect with other carcinogenic molecules to promote the development of CRC. H. pylori-induced inflammatory changes in colonic mucosa [44] is probably related to inflammation and cytokine release. Considering that chronic inflammation caused by H. pylori infection could increase gastrin secretion [45, 46], in our study, Hp-IgG was regarded as an adjustment factor in the analysis of G-17. In stratification analysis, we found G-17 was only significantly associated with CRC in the Hp-IgG negative subgroup (\(P<0.001\)). This finding is different from the results obtained in similar studies conducted in different gastric disease populations. In addition to H. pylori infection, the level of gastrin in serum is affected by many factors, such as age and gender, etc. Our results show that H. pylori infection has a lower effect on serum gastrin levels in CRC cases than in the controls, suggesting that the risk effect of G-17 on CRC was more obvious in the H. pylori negative population.

We explored the association of PGI, PGII, PGI/II ratio, G-17 and Hp-IgG levels with serum tumor biomarkers. The results showed that G-17 was associated with CA125 positivity (\(P=0.005\)). Hp-IgG was associated with CA125 (\(P=0.024\)) positivity. However, no statistically significant association was observed in the serum levels of PGI, PGII and PGI/II ratio with CEA, AFP, CA125, CA153 or CA199.CA-125 was a representative biomarker of ovarian cancer and was expected to be applied as a screening tool in patients at risk of ovarian cancer. CA125 and pro-gastrin-releasing peptide (ProGRP) were reported to be increased simultaneously in patients with advanced lung adenocarcinoma[47]. G-17, which can promote the secretion in the gastrointestinal tract, and the release of insulin and calcitonin, may also increase the serum level of CA125 related to endocrine system and hormone levels. The association between G-17 and CA125 in CRC suggested that G-17 might play an important role in hormone regulation of CRC. It not only has a possible diagnostic value but also could be beneficial to CRC therapy from the perspective of endocrinology, which is a very interesting topic in further investigation. Most cancer derives from chronic inflammation and tumor microenvironment, which is an important participant in the neoplastic process mainly induced by inflammatory cells. H.pylori infection might affect inflammation status. In view of the association between H.pylori and tumor biomarkers in CRC, we speculate that H.pylori may also play a role in colorectal carcinogenesis.

Lastly, we analyzed the association between serological marker levels and clinicopathological parameters of CRC. However, no significance was indicated between gastric function indicators, Hp-IgG and any of the CRC clinicopathological parameters assessed.

Some limitations should be acknowledged in our study. First, the study design is retrospective and observational, which has inherent limitations. Given that serum samples were collected once the CRC was present, the disease could have caused the modification in the markers instead of the opposite hypothesis. As a result, it is inevitable to discard a possible reverse causation. Secondly, all the subjects are hospital-based, which may cause selection bias. The controls were volunteering attending to the Medical Examination Department, thus they had more symptoms than the general population bringing them to seek health checking, which might lead to some underestimation of a possible association between the markers studied and CRC. Moreover, the low participation rate among controls could also increase the risk of selection bias, resulting in the difference of serum markers level between study subjects and general population. Thirdly, we had not data on potential confounding factors, especially the information about other CRC risk factors including obesity, diet, smoking, physical activity, family history, red and processed meat intake, fruit and vegetables intake, etc. Furthermore, our research is only focused on the association study without in-depth investigation about involved mechanisms. In the future, functional studies are needed to explore the specific mechanism to verify our results.
In summary, we explored the clinical significance of serum markers reflecting gastric function and \textit{H. pylori} infection in colorectal cancer. It was shown that the aberrant indicators PGII, G-17 and Hp-IgG might be associated with an increased CRC risk; G-17 and Hp-IgG were associated with some tumor biomarkers; Therefore, the serum markers reflecting gastric function and \textit{H. pylori} infection might serve as indirect indicators of intestinal function, and may provide additional opportunities to develop complementary therapies that target the inflammatory microenvironment of CRC.

**Abbreviations**

CRC: colorectal cancer; GC: gastric cancer; IgG: immunoglobulin G; OR: odds ratio; CI: confidence intervals; ELISA: enzyme-linked immunosorbent assay; Hp: Helicobacter pylori; PG: pepsinogen; G-17: gastrin 17; IM: intestinal metaplasia; ENTD: extranodal tumor deposits.

**Supplementary Material**


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**Ethics Committee Approval and Patient Consent**

The study was approved by the Ethics Committee of the First Hospital of China Medical University and written informed consent was obtained from all participants.

**Competing Interests**

The authors have declared that no competing interest exists.

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