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# *Helicobacter pylori* infection in patients with colorectal adenocarcinoma and its association with tumor grade and location: a cross-sectional study

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## ABSTRACT

**Aim**: Given the positive results of some research, this study aimed to explore the relationship between the presence of *Helicobacter pylori* (HP) in gastric histopathology and the location and grade of tumors in an institutional sample of patients diagnosed with colorectal cancer (CRC).

**Background**: Epidemiological studies have been conducted to investigate the association between HP infection and CRC.

**Methods**: This cross-sectional study retrieved data from the hospital database, considering inclusion criteria and medical record availability for patients who underwent both endoscopy and colonoscopy and were diagnosed with CRC. Patients were grouped based on tumor grade and location and compared regarding the presence or absence of HP pathogen in endoscopic biopsy direct smears.

**Results:** Data from 241 patients were available, 220 of whom had adenocarcinoma. A statistically significant relationship between tumor differentiation grade and HP positivity was observed (P= 0.001). Each 1-level increase in grade was associated with 2.2 times higher odds of HP positivity. No significant relationships existed in the analysis of tumor location related to HP positivity.

**Conclusion**: In colorectal cancer patients, the presence of the HP pathogen may be linked to a higher likelihood of high-grade colorectal cancers. This finding needs to be explored in screening cohorts.

**Keywords**: *Helicobacter pylori*, Colorectal cancer, Tumor grade.

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## Introduction

The incidence of colon cancer in populations is attributed to several environmental factors such as lifestyle, intestinal inflammation, and aging, while inherited genetic disorders are responsible for a small fraction of cases. The majority of CRCs arise from adenomatous polyps, highlighting the significance of early detection, as removal of these malignant precursors acts in reducing mortality rates associated with cancer (1). Alternative methods for the prevention and early detection of colon cancer may further mitigate its impact on public health.

*Helicobacter pylori* (HP) is a gram-negative, microaerophilic bacterium that predominantly inhabits the deep regions of the gastric mucosa, positioning itself between the mucus and the gastric epithelium (2). Exposure to this pathogen can be diagnosed using non-invasive methods, including rapid urease assays, polymerase chain reactions, and enzyme-linked immunosorbent assays (ELISA). Alternatively, invasive techniques such as endoscopy, tissue staining, and cultivation on specialized media can confirm active disease (3). HP is a bacterium known to cause various gastric diseases, including gastritis, peptic ulcers, and gastric cancer (4). Various studies have explored atrophic gastritis induced by HP (5) or antibody responses to surface proteins of H. pylori, particularly HcpC and VacA (6). Due to its fundamental role in the development of precancerous lesions in gastric cancer,

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HP is classified as a class 1 carcinogen, but due to the observed risk of colon adenoma or cancer linked to HP, new mechanisms have been postulated to explain the impact of this bacterium in a remote environment, attributed to the production of certain metabolites (7). Several studies establishing a connection between the presence of HP in the stomach or intestine and colon cancer or colon polyps (8-13), supported by a few meta-analyses (14-16), have been conducted to investigate the association between HP infection and colorectal cancer (17). Based on existing evidence of the link between HP infection and colorectal adenoma with aggressive pathologic features (9, 18), this study aims to investigate the relationship between positive HP identification in gastric pathology slides and the location and grade of tumors in patients diagnosed with colorectal adenocarcinoma.

## Methods

The present study is a cross-sectional study performed in Firoozgar Hospital, a tertiary educational hospital of the Iran University of Medical Sciences. Retrospective data were extracted from hospital information system's electronic database. The study population comprised outpatients who visited the gastroenterology clinic, and inpatients from 2019 to 2020 who had been candidates for both endoscopy and colonoscopy following the presentation of gastrointestinal symptoms. Patients were included in the study by census sampling; all had a documented colonoscopy, which ultimately led to a confirmed diagnosis of colorectal tumors, and an HP sampling during endoscopy. Data, which included demographic information, pathology type, grade, and location of the colorectal tumor based on surgical or colonoscopy specimen reports, was collected. If any relevant information was unknown, data was retrieved from medical documents, while missing data was allowed. Adenocarcinoma histology was only included in the analysis, and patients with a known or explored history of non-skin cancer other than colorectal cancer were excluded from the study.

## Histological evaluations

The specimens had been inspected by a senior gastrointestinal pathologist at the Department of Pathology, Firoozgar Hospital, Tehran, Iran. As part of the educational protocol validation, all slides were reviewed independently by at least two senior residents and were approved by the attending pathologist in charge. Tumor grading was classified based on the College of American Pathologists' criteria into a three-tire system as follows: Grade 1 Well differentiated (>95% gland formation), Grade 2 Moderately differentiated (50-95% gland formation), and Grade 3 Poorly differentiated (<50% gland formation) (19). *Helicobacter pylori* infection was detected in endoscopic biopsies through hematoxylin and eosin and/or Giemsa histological staining.

This study was approved by the Ethics Committee of Iran University of Medical Sciences under registration number IR.IUMS.REC.1400.806

## Statistics

The qualitative descriptive statistics are expressed in mean, standard deviation, and percentage. Comparisons between qualitative variables were made by the Chi-square test or the Exact Fisher test. Chi-Square Test for Trend (Cochran-Armitage Test) was used to test if HP positivity has a linear relation with grade. An ordinal logistic regression was used to confirm the results. Likelihood ratio test (model fit) and the Brant test (proportional odds assumption) were used in this regard. Statistical analysis was performed using SPSS V.24 software with a significance level of less than 0.05.

DEGs were identified in both datasets using the following criteria: Benjamini & Hochberg adjusted P-value < 0.05, and a log fold change (Log FC) > |0.5|. A total of 246 common DEGs between the two datasets were used for subsequent analyses.

## Results

## Descriptives

Data was initially collected from 308 records, while nine of the cases were duplicates and were deleted, a total of 258 patients were included in the study. The pathology of 220 (85.2%) patients showed that the colorectal tumor was adenocarcinoma. The pathology of the remaining 11 cases revealed adenomas (4.2%), neuroendocrine tumor (1.1%), and squamous cell carcinoma (0.3%), and six samples were recorded as uncategorized cancers (2.3%). The average age of the cancer patients was 56.4, and 96 (37%) of them were women. Seventy-five patients were positive for HP by

**Table 1.** Site of colorectal cancers and gastric *helicobacter pylori* positivity.

| Anatomical Site | *H. pylori* (-) | *H. pylori* (+) | Total Patients | % Positive |
|---|---|---|---|---|
| Cecum | 7 | 4 | 11 | 36.4% |
| Appendix | 5 | 1 | 6 | 16.7% |
| Ascending Colon | 25 | 13 | 38 | 34.2% |
| Hepatic Flexure | 7 | 7 | 14 | 50.0% |
| Transverse Colon | 11 | 3 | 14 | 21.4% |
| Splenic Flexure | 4 | 1 | 5 | 20.0% |
| Descending Colon | 16 | 7 | 23 | 30.4% |
| Sigmoid Colon | 45 | 26 | 71 | 36.6% |
| Rectum | 39 | 16 | 55 | 29.1% |
| Overall | 159 | 78 | 237 | 32.9% |

**Table 2.** Relation between grade of colorectal cancers and gastric *helicobacter pylori* positivity

| Grade | *H. pylori* (-) | *H. pylori* (+) | Total | % Positive | p-value (vs. low) |
|---|---|---|---|---|---|
| Low | 88 | 22 | 110 | 20.0% | Reference |
| Moderate | 32 | 17 | 49 | 34.7% | 0.03* |
| High | 30 | 27 | 57 | 47.4% | <0.001* |

Test for Trend: $p < 0.001$ (Cochran-Armitage).

direct smear, and about one third (31.6%) of those with colorectal adenocarcinoma were HP positive. Data related to tumor site or tumor grade were absent in 8.1% of patients.

Analyses were continued in the adenocarcinoma group. Table 1 shows the distribution of tumor sites in the sample. The hepatic flexure site had the highest HP positivity rate (50%), while the appendix had the lowest (16.7%). The transverse colon and splenic flexure show relatively low positivity rates (<25%). The HP positivity was almost equally distributed between the midgut and hindgut regions.

## Comparative analyses

There was no significant relation between gender and HP positivity (p> 0.05), the relation between adenocarcinoma tumor location and HP positivity was non-significant ($\chi^2 = 6.82$, df = 8, p = 0.556), but there was a significant relation between HP positivity and adenocarcinoma tumor grade. Table 2 shows a significant relation between increasing histological grade (ordinal variable) and HP positivity (binary outcome), demonstrating that HP positivity increased significantly with higher histological grade (p-trend < 0.001). Since grade was an ordinal predictor, we used ordinal logistic regression (proportional odds model) to confirm the trend observed in the chi-square test. High-grade tumors had 47.4% positivity vs. 20.0% in low-grade (p < 0.001). Moreover, the results showed that each 1-level increase in grade (e.g., low to moderate) was associated with 2.2 times higher odds of HP positivity in direct smear samples of the gastric mucosa (OR = 2.20, 95% CI: 1.50–3.23, p < 0.001).

## Discussion

This study aimed to find relations between colorectal tumor characteristics, grade, and tumor site in particular, and the results of HP direct smear of the gastric sample. The main finding of this study was the significant trend, meaning higher grades correlate with higher HP infection rates detected by direct smear. Moreover, our study demonstrates a robust, grade-dependent increase in HP prevalence, with high-grade tumors showing 2.2-fold higher odds per grade. These findings align with hypotheses that poorly differentiated tumors may favor HP persistence and collectively underscore the potential association of HP with high-grade colorectal tumors. Notedly, the relation between the location of colorectal adenocarcinoma and HP positivity was not detected.

While evidence for a possible linkage between HP and colorectal premalignant or malignant lesions is abundant, the strength of the causative associations is weak from the epidemiologic point of view (7), and it remains an intriguing topic of investigation. A number of cross-sectional studies have reported an association: The presence of HP in gastric histopathology was linked to CRC when compared to controls, and meta-analyses have also detected modest relations (17). Some of the studies were derived from large screening records, making the link more probable; Adjusted multivariate

analysis of a cross-sectional serological screened population (10), and another clustered co-occurrence of CRC and HP after adjusting for shared risk factors after screening, suggest potential independent relationships between both conditions (20). Adjusted hazards of a screening cohort also showed that both HP seropositivity and biopsy-proven HP were associated with colorectal polyps and cancers in a median follow-up of 3 years (21). Though the underlying mechanisms of this relation have not been clearly understood, the HP pathogen has been detected in different types of colonic polyps and cancer (21-23), as it has been demonstrated that HP may travel through the intestine and directly interact with the colonic mucosa (9). Subsequently, flora alterations, inflammatory response, or hormone and toxin mediators may attribute to the linkage (17). Destruction of the colon epithelium may occur due to the direct effect of the microbiome or HP-induced immune alterations (24). Also, changes in colonic microbiota may occur indirectly due to HP-induced atrophic gastritis (25), followed by the induction of hypergastrinemia, which may stimulate the growth of tumoral cells in the colon (4). Furthermore, the detection and elimination of risk factors play a huge role in reducing the prevalence of this cancer. Even surprisingly, HP eradication has been linked to reduced incidence of colonic adenomas (26). Because of all of these possibilities, it is likely that HP detection is causally linked to CRC, and it might justify an additional HP screening and surveillance program in patients or regions at high risk for CRC. In particular, most CRCs are sporadic, without significant hereditary risk. Therefore, environmental factors sensibly contribute considerably to the variation of incidence (1). Although the incidence of CRC differs in eastern and western countries, a meta-analysis showed that the risk of CRC was affected by HP in different ethnicities, including Asian, European, and American populations (27). Another report explained the variety of relatedness of HP to CRC incidence in different regions of East Asia (28). It can be concluded that differences in patient and tumor features and relatedness to HP may be due to different study populations and regional prevalence patterns.

Studies have rarely investigated the relationship of direct smear HP positivity with the features of colorectal neoplasia in affected patients. Accordingly, our findings of HP positivity in those who have high-grade cancers were novel. In this regard, one study showed that HP infection was found to be associated with cancer or more advanced, larger than 1 cm, non-tubular, colorectal adenomas (9), and another study showed that only higher-grade polyps were associated with HP (18). Larger size and increased number of adenomas were related to HP positivity in a retrospectively explored large dataset (28). Though hard to confirm, the findings above may suggest a possible effect of HP on tumor aggressiveness.

The relation between the location of colorectal tumors and HP was not detected in our sample, which was a similar finding to some other studies (9, 29). The relation has been contradictorily reported as gastric HP infection was positively associated with an increased risk of proximal colorectal adenomatous polyps (30), which was supported by a meta-analysis (31). Some theories explain these relations by suggesting that the increased production of bile acids and subsequent DNA damage in the proximal colonic mucosa increase the risk of polyps and malignancies in this region (25). Oppositely, in other studies HP infection was associated to risk of distal CRC, confined to the left colon (24), or distal colon and rectum (30), albeit HP exposure was detected by serologic examination in these two studies, the method of HP detection of serological versus non-serological affected the relation between HP and CRC in a metanalysis, with a stronger association for non-serological methods (32). Some models have demonstrated that increased gastrin secretion caused by HP has a mitogenic effect and selectively acts on the distal colon (30). CRC has been emphasized as phenotypes with discriminant etiologies and genetic variations in future well-designed studies exploring the affected site and mechanisms of virulence of HP. will expand our understanding about the causality of this coincidence.

This study was limited by the cross-sectional nature and small study population. Without accounting for known causative factors, the possibility of residual confounding cannot be ruled out. The lack of inclusion of known or potential risk factors for colorectal cancer, such as dietary habits, smoking status, BMI, family history, and comorbidities, which could influence both HP infection and CRC incidence, is notable. There is a potential for residual confounding of not recording antibiotic use, but as the method for HP infection was the presence in direct smear, this factor may have the least

impact. Therefore, validation of the present findings should be executed in multi-center cohorts since the cross-sectional nature cannot discuss causality. The strength of the current study is not relying on serologic exam of HP detection, which is hampered by low sensitivity and specificity.

Considering the complexity of colorectal cancer as a heterogeneous disease, and treatment differences according to its different phenotypes, further research is necessary to clarify the exact mechanisms and relationship between HP and CRC. These collective findings emphasize the importance of continued research in this field to better understand the implications on CRC prevention, diagnosis, and treatment.

## Conflict of interests

The authors declare that they have no competing interests.

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