ROLE OF HELICOBACTER BACTERIA IN COLITIS AND COLO-RECTAL NEOPLASMS HISTOPATHOLOGICAL AND IMMUNOHISTOCHEMICAL STUDY

Thesis

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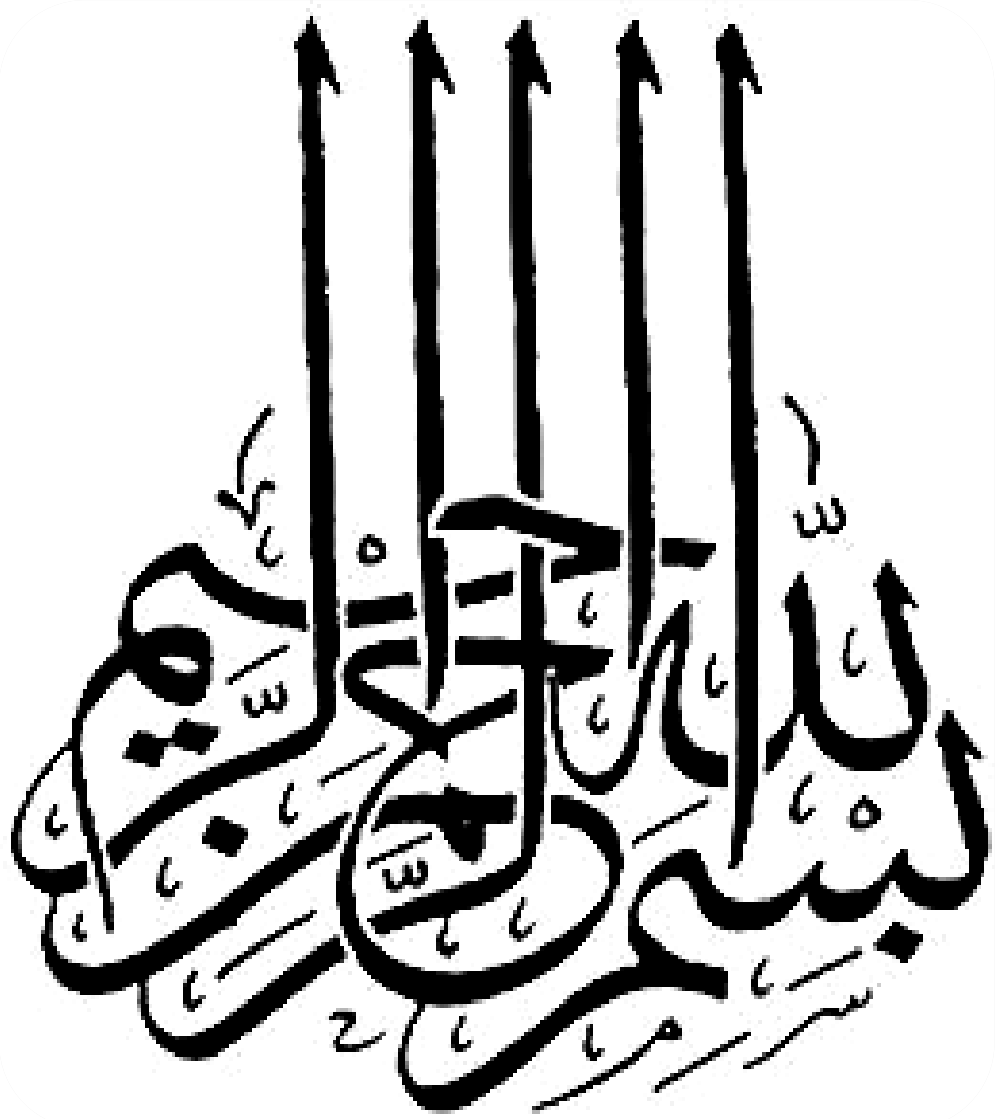

﴿ قَالُواْ سُبْحَانَكَ لاَ عِلْمَ لَنَا إِلاَّ مَا عَلَّمْتَنَا إِنَّكَ أَنتَ الْعَلِيمُ الْحَكِيمُ ﴾

(البقره ٣٢)

صدق الله العظيم

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ABSTRACT

This study aims to determine the role of *Helicobacter* organisms in the development of colitis or colorectal neoplasia and to correlate *Helicobacter* immunohistochemical positivity with other clinicopathologic parameters. This retrospective study was conducted on fifty cases, including 10 (20%) cases of normal colon, 15 (30%) cases of colitis, 10 (20%) cases of colonic tubular adenoma and 15 (30%) cases of colorectal carcinoma. Immunohistochemical detection method rather than routine histochemistry with Giemsa was used for the detection of *H. pylori.* This study showed that:

- Anti-*H.Pylori* antibodies were positive in 14 (28%), however 36 (72%) were negative.
- Among normal participants, anti- *H. Pylori* antibody staining was positive in 2 (20%) and negative in 8 (80%).
- Among patients with colitis, anti- *H. Pylori* antibody staining was positive in 5 (33.3%) and negative in 10 (66.7%).
- Among patients with adenoma, anti- *H. Pylori* antibody staining was positive in 4 (40%) and negative in 6 (60%).
- Among patients with carcinoma, anti- *H. Pylori* antibody staining was positive in 3 (20%) and negative in 12 (80%).
- The prevalence of *H. Pylori* positivity is not statistically significant in cases of normal colon, colitis, tubular adenoma or carcinoma.
- However risk estimation as determined by Odds ratio showed that *H. Pylori* positivity is most likely present in specimens with colitis **(Odds ratio = 1.444)** and adenoma **(Odds ratio= 2.000**).

Keywords: (Helicobacter bacteria – Colitis – Colorectal neoplasms – Immunohistochemistry)

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LIST OF ABBREVIATIONS

AC I	Amesterdam Criteria I
ACF	Aberrant Cryptic Foci
AJCC	American Joint Comitee on Cancer
APC	Adenomatous Polyposis Coli
BAX	Bcl-2–associated X protein
CD	Crohn's Disease
CEA	Carcinoembryonic Antigen
CMV	Cytomegalovirus
c-myc	Oncogene
CRC	Colorectal Carcinoma
CRM	Circumfrential Resection Margin
CTC	Computed Tomographic Colonography
DALM	Dysplasia Associated Lesion or Mass
DCBE	Double Contrast Barium Enema
DCC gene	Deleted in colon cancer Gene
DNA	Deoxyribonucleic acid
EHEC	Enterohemorragic *E. coli*
EIEC	Enteroinvasive *E. coli*
FAP	Familial Adenomatous Polyposis
FOBT	Focal Occult Blood Test
FSIG	Flexible Sigmoidoscopy
GIT	Gastrointestinal Tract
H.Pylori	Helicobacter Pylori
HNPCC	Heriditary Non-polyposis Colorectal Cancer
HSP	Henoch Shonlein Purpura
IBD	Inflammatory Bowel Disease
IGF2	Insulin-like growth factor 2
K-ras	Oncogene

LOH	Loss of Heterozygosity
MAC	Mucinous Adenocarcinoma
MAP kinase	Mitogen-activated protein kinase
MMP7	Matrix Metalloproteinase 7
NEC	Necrotizing Enterocolitis
NEC	Neuroendocrine Carcinoma
NET	Neuroendoendocrine Tumour
P16	Tumor suppressor gene
P53	Tumor suppressor gene
PMNs	Polymorph Nuclear Leucocytes
PPARs	Peroxisome proliferator-activated receptors
SCC	Squamous Cell Carcinoma
SMAD4	Tumor suppressor
TGF-β	Transforming growth factor beta
TGFβR-II	Transforming growth factor beta receptor-II
TME	Total Mesorecatal Excision
UC	Ulcerative Colitis
UICC	Union International Contre Le Cancer
WHO	World Health Organization

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INTRODUCTION

The number of species in the genus Helicobacter has rapidly expanded over the past decade. The genus now includes at least 24 formally named species as well as numerous other helicobacters awaiting formal naming **(Fox, 2002).**

Helicobacter pylori (H.pylori) is the best known and the most important in terms of global impact on human disease. It infects 50% of the world population and its prevalence varies widely in different parts of the world with average rates of 40–50% in western countries, rising to >90% in the developing world **(Peek and Blaser, 2002).**

H.pylori is a Gram-negative bacterium that has become well adapted to the human stomach via interaction with gastric epithelial cells **(De Luca and Iaquinto, 2004)**. Chronic gastric infection with H. pylori causes inflammation and several gastric pathologies, including gastric ulcers and gastric cancer **(Lochhead and El-Omar, 2007).**

Compelling evidence from epidemiological, histopathological and animal studies has linked H.pylori infection to the subsequent development of gastric cancer **(Uemura *et al.*, 2001).**

Despite the established relationship between H. pylori and gastric pathologies, the association between H. pylori and colorectal cancer is much less clear. Epidemiologic studies have used serology, PCR methods, C-urea breath tests, and circulating gastrin levels to examine colorectal neoplasia in relation to H. pylori infection and have produced conflicting results **(Andrea *et al.*, 2008).**

Infection of colorectal tissue with H. pylori may not be directly responsible for an increased risk of colorectal cancer but rather the byproducts of a gastric H. pylori infection **(Hartwich *et al.*, 2001).** One theory stems from the fact that gastric H. pylori infection increases serum

levels of gastrin leading to hypergastrinemia **(Mulholland *et al.*, 1993).** Because hypergastrinemia is hypothesized to have proliferative effects on intestinal mucosa **(Sobhani *et al.*, 1993).** A positive association has been found between hypergastrinemia and colorectal neoplasia **(Georgopoulos *et al.*, 2006).**

Carcinogenesis via H. pylori involves inflammation, as well as deregulation of the cell cycle via the H. pylori protein, cytotoxin-associated gene A (CagA), which binds and activates SHP2 (a human phosphatase that can act as an oncoprotein) resulting in cell growth and motility **(Lochhead and El-Omar, 2007).**

Associations between neoplastic colorectal lesions (adenomas and carcinomas) and H.pylori were based on indirect evidence such as studies correlating these lesions with increased CagA+ levels **(Hartwich *et al.*, 2001)** or increased gastrin **(Konturek *et al.*, 2002)** or, direct correlation with H.pylori seropositivity **(Fujimori *et al.*, 2005).** Other studies have failed to demonstrate this association based on seropositivity **(Limburg *et al.*, 2002).**

Enterohepatic helicobacters are non H. pylori helicobacters which naturally colonise the intestinal crypts and are often associated with diarrhea, can cause bacteraemia and systemic disease including colonisation of the biliary tract and induction of cholecystitis and hepatitis (and in some cases hepatic cancer). Immunocompromised hosts are particularly susceptible to these microorganisms **(Solnick and Schauer, 2001).**

It is possible that *Helicobacter* species are under recognized causes of infective diarrhea in humans. Helicobacters cultured from human diarrheal samples include *H cinaedi, H canis, H pullorum*, *Helicobacter fennelliae, Helicobacter Canadensis*, *Helicobacter rappini* and other unclassified but related organisms **(Fox, 2002).**