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TOPIC HIGHLIGHT

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Helicobacter pylori and gastric cancer: Indian enigma

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Abstract

Helicobacter pylori (*H. pylori*) is a gram negative microaerophilic bacterium which resides in the mucous linings of the stomach. It has been implicated in the causation of various gastric disorders including gastric cancer. The geographical distribution and etiology of gastric cancer differ widely in different geographical regions and *H. pylori*, despite being labeled as a grade I carcinogen, has not been found to be associated with gastric cancer in many areas. Studies in Asian countries such as Thailand, India, Bangladesh, Pakistan, Iran, Saudi Arabian countries, Israel and Malaysia, have reported a high frequency of *H. pylori* infection co-existing with a low incidence of gastric cancer. In India, a difference in the prevalence of *H. pylori* infection and gastric cancer has been noted even in different regions of the country leading to a puzzle when attempting to find the causes of these variations. This puzzle of *H. pylori* distribution and gastric cancer epidemiology is known as the Indian enigma. In this review we have attempted to explain the Indian enigma using evidence from various Indian studies and from around the globe. This review covers aspects of epidemiology, the various biological strains present in different parts of the country and within individuals, the status of different *H. pylori*-related diseases and the molecular pathogenesis of the bacterium.

Key words: Gastric cancer; Gastric diseases; *Helicobacter pylori*; p53 mutation; Carcinogen

Core tip: This review highlights the unusual finding of low prevalence of gastric cancer despite high prevalence of *Helicobacter pylori* in India and its probable causes including diet and genetic variations as seen in Indian patients. This finding is attributed to increased genetic resistance in addition to a vegetarian diet rich in antioxidants.

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INTRODUCTION

It has been 30 years since the discovery of *Helicobacter pylori* (*H. pylori*) in 1983 by Australian physicians Robert Warren and Berry Marshal[1] In view of the various epidemiological studies worldwide, the International Agency of Cancer classified *H. pylori* as a Class I carcinogen for gastric cancer in 1994[2]. Since then the bacterium is thought to be one of the causative factors in the development of gastric cancer.

H. pylori is a gastric pathogen that colonizes approximately 50%-60% of the world's population[3]. Infection with *H. pylori* causes chronic inflammation and signifi-

cantly increases the risk of developing duodenal and gastric ulcer disease and gastric cancer. *H. pylori* infection is the strongest known risk factor for gastric cancer, which is the second leading cause of cancer-related deaths worldwide[4].

Studies in Asian countries such as Thailand, India, Bangladesh, Pakistan, Iran, Saudi Arabian countries, Israel and Malaysia, have reported a high frequency of *H. pylori* infection co-existing with a low incidence of gastric cancer[5-8].

This review aims to explain this Indian enigma through various studies performed in past two decades in different parts of the country.

EPIDEMIOLOGY

Over past few decades there have been many studies related to gastric cancer which showed marked geographical variations with high risk areas in Japan, China, Eastern Europe, and some countries in Latin America. Low risk regions are North America, India, Philippines, Africa, some parts of Western Europe and Australia[9].

Various epidemiological studies in India have shown a high incidence of gastric cancer in South India as compared with North India[10]. The prevalence of *H. pylori* infection is high (49.94%-83.30%) in India, but the incidence of gastric cancer is comparatively low indicating mixed results for the association between *H. pylori* and gastric cancer. Human epidemiological studies have shown mixed results with a definite association between *H. pylori* and gastric cancer in approximately 50% patients, and a negative relationship in the remaining patients[11,12].

In North India the prevalence of *H. pylori* in patients with gastric carcinoma was assessed and correlated with gross appearance and histological types[13]. The prevalence of *H. pylori* in controls was slightly higher than that in the patient group (80% *vs* 78%). Diffuse type gastric cancer was more common than intestinal type and the prevalence of *H. pylori* was greater in diffuse type gastric cancer than in intestinal type (86% *vs* 68%). A significant association between *H. pylori* and grades of gastritis was noted ($P < 0.01$) in controls as well as in the patient group, but failed to show a significant association with tumor grade, intestinal metaplasia, site of tumor and age of patient. It was inferred that the prevalence of *H. pylori* infection is not directly associated with the pathogenesis of gastric cancer, but may act as a co-carcinogen by damaging the mucosa and thereby making it more susceptible to the effects of a carcinogen.

Quigley *et al*[14] in their review stated that human epidemiological studies have produced mixed results with an association between *H. pylori* and gastric cancer in 50% patients, while the remaining patients showed a negative relationship.

Dietary variation in the Indian population

Diet plays an important role in gastric carcinogenesis. In India, southern and eastern parts of the country have a gastric cancer frequency approximately 4 times higher than that in northern parts of the country[9,15]. A high incidence of gastric cancer in both males (50.6%) and females (23.3%) has been reported from Mizoram[16]. Non-vegetarian foods, particularly fish, are very common in the east Indian diet, which is also spicy with more salts. Pickled food, high rice intake, spicy food, excess chili consumption, consumption of high-temperature foods, smoked dried salted meat, use of soda and consumption of dried salted fish have emerged as significant dietary risk factors for gastric cancer[17-21]. The diet in south India is similar to that in eastern parts with rice, fish, excess spice and salt commonly eaten providing an explanation for the higher incidence of gastric cancer in these regions.

In contrast, the north Indian diet is mainly wheat-based and a greater proportion of people are vegetarian with a high intake of fruits and spices like turmeric[22,23] and garlic[24,25] which are known to have anti-cancerous properties. Dietary habits, especially high intake of curcumin and a vegetarian diet, could be one explanation for the Indian enigma[26,27].

H. PYLORI STRAINS IN INDIA

The study of *H. pylori* genomics began in August 1997 with the publication of the complete genome of *Helicobacter pylori* 26695, which was cultured from a gastritis patient in the United Kingdom[2,28]. Recent technological advancement has made sequencing of the genome more accessible and less costly resulting in a rapid increase in the number of *H. pylori* isolates sequenced, including some of the important laboratory strains[29]. Up to March 2013, 43 complete genomes and 198 draft genome sequences had been deposited in GenBank for public access, and the federated genomic databases are still growing.

Based on the country of origin of the source patient: 18 were from North and South America, 14 from Far East Asia (Japan/South Korea/China), 11 from Europe, 10 from Malaysia, six from Africa, four from India, and one from Australia. Based on available data of the complete genomes in GenBank, the average size of an *H. pylori* genome was estimated to be 1.62 Mb (1.51-1.71 Mb) with a gastric cancer (GC) content of 38.92% (38.4%-39.3%). The average *H. pylori* genome was predicted to consist of 1590 (1429-1749) open-reading frames encoding 1532 (1382-1707) proteins[29].

Between 2012 and 2013, two *H. pylori* strains were isolated from duodenal ulcer patients in Bangalore (NAB47) and Delhi (NAD1) in India[10]. Based partly on these conventions, Indian *H. pylori* isolates have been shown to have European origins[11] and are widely held to be mostly innocuous or only mildly pathogenic, unlike their highly virulent Far East Asian counterparts (which may be linked to the high incidence of gastric cancer). It is certain that these genomes representing Indian patients will rekindle our understanding of the genetic makeup

and evolutionary relationships of this pathogen in India.

MULTIPLE STRAINS AT THE SAME SITE

H. pylori exhibits conspicuous genetic diversity as evidenced by an apparently unlimited number of unique strains that differ in genome size, gene order, genetic content, and allelic profiles[12]. *H. pylori* exhibits more frequent recombination events with heterologous strains than any other known bacterial species[13]. Microarray and nucleotide sequence analysis of strains isolated longitudinally from the same patient imply that this recombination is a continuous event[14,30].

Studies from Europe and Western countries showed that almost all strains of *H. pylori* isolated from different sites in the stomach of individual patients show homogeneous DNA profiles. In contrast, Mexican and Chinese populations are infected with genetically heterogeneous strains with high infection rates. In India, the prevalence of *H. pylori* infection is high[8,24,31] and the chances of infection and re-infection of strains in a single host is relatively high as compared to Western populations. In addition, a similar trend in heterogeneity of strains has been shown in the Indian continent[32]. Genetic exchanges among mixed bacterial populations may generate a more competitive strain to adapt to a particular host thereby propagating a more virulent strain. In India, the prevalence of *H. pylori* infection is much higher as compared to the most western countries and almost all infected cases were found to carry multiple *H. pylori* strains[32].

PEPTIC ULCER DISEASE

Researchers have reported the role of *H. pylori* infection in the pathogenesis of peptic ulcer and stomach cancer in India, and some have reported no association between stomach cancer and *H. pylori* infection[33-39]. In a recent study of 190 peptic ulcer patients, 35 stomach cancer patients, and 125 controls, the author concluded that *H. pylori* infection is associated with peptic ulcer disease. Lower socioeconomic status, consumption of restaurant food, meat, nonfiltered water, and smoking are risk factors for *H. pylori*. Consumption of meat, fish, and a family history of peptic ulcer are risk factors for peptic ulcer. Consumption of chili, peppers and concurrent parasite infestation appears to be protective against *H. pylori*[38].

The epidemiology of peptic ulcer disease (PUD) in India differs from that in the West. It may have undergone a change with recent improvements in hygiene and availability of potent antisecretory and ulcerogenic drugs. In a time trend study of *H. pylori* infection and PUD, the frequencies of duodenal and gastric ulcer disease in study groups were compared. Of the 30,216 patients (mean age: 41.7 ± 12.7 years, 34% females) during the six study periods, 2360 (7.8%) had PUD. The frequencies of both duodenal ulcer and gastric ulcer declined from 1988 to 2008, *i.e.*, from 12% to 2.9% and from 4.5% to 2.7%, respectively ($P < 0.001$ for each). The decline was more marked for duodenal ulcer, and the ratio of duodenal to gastric ulcer declined from 2.7 in 1988 to 1.1 in 2008. The epidemiology of PUD in India may have changed in the past two decades with the incidence of duodenal ulcer declining more rapidly than that of gastric ulcer[40].

In a recent review it was concluded that *H. pylori* is the primary cause of duodenal ulcer supported by strong evidence in the literature linking *H. pylori* etiologically to duodenal ulcer and reports on eradication therapy of *H. pylori* in preventing relapse of uncomplicated and complicated duodenal ulcer[41].

GC

GC is the third most common cancer in India and the second leading site of cancer occurrence world-wide. The incidence of GC is 4 times higher in South India than in North India[42]. An understanding of the molecular mechanism of gastric carcinogenesis and its relationship to *H. pylori* improved in the last decade. Most studies showed either no or a negligible effect of *H. pylori* in gastric carcinogenesis in India.

Misra *et al*[42] studied the effect of *H. pylori* on the proliferative activity of gastric epithelium by studying Ag-NOR counts, but found no significant difference in normal controls, inflammatory lesions and cancer, concluding that *H. pylori* has no direct effect on the proliferative activity of gastric epithelium. A prospective study reported the association of microsomal epoxide hydrolase exon 3 Tyr113His and exon 4 His139Arg polymorphisms with gastric cancer in India and concluded that 113Tyr-139Arg was associated with GC in the presence of *H. pylori*, in its absence, it appeared to be protective. However, exon 3113His was associated with GC even in the absence of *H. pylori* infection[43]. The role of cytochrome P450 (CYP), a polymorphic carcinogen-activating enzyme, CYP2E1, CYP1A2 (rs762551), and CYP1A1 (rs4646903) polymorphisms in association with *H. pylori* infection in gastric carcinogenesis was studied and it was found that the presence of CYP2E1 (96-bp insertion) is associated with increased risk of GC even in the absence of *H. pylori*. CYP1A2 CC or CT is associated with a reduced risk of GC[44]. Another study showed that p53 gene mutation was present in 4.6% of the study population. This mutation was significantly higher in GC when compared with PUD and non-ulcer dyspepsia (NUD), and was independent of *H. pylori* infection indicating a role for p53 gene mutation in gastric carcinogenesis, independent of *H. pylori* infection. K-ras gene mutation was not seen in GC and PUD in Indian patients[45].

Repression of Runt-related transcription factor 3 (*Runx3*) gene, a tumor suppressor gene, has been shown to be involved in *H. pylori*-associated gastric carcinogenesis and cancer development[46]. The study was undertaken to investigate Runx3 intronic T/A polymorphism (rs760805) in *H. pylori*-infected patients and uninfected controls of the Tamil Nadu region, South India. In addition, *Runx3* gene expression, HK alpha (H, K-ATPase)

gene expression and the methylation status of the Runx3 CpG island were determined. Neither significant repression of *Runx3* and HK alpha genes nor methylation were detected in positive patients, suggesting a lack of involvement of this tumor suppressor as a risk factor in *H. pylori*-associated gastric carcinogenesis in the South Indian population studied.

Tobacco-smoking was found to be an important risk factor for the high incidence of stomach cancer in Mizoram. Meiziol (local cigarette) smoking was a more important risk factor than other tobacco related habits. Polymorphisms of *GSTM1* and *GSTT1* genes appeared to be effect modifiers. Persons habituated to tobacco smoking and/or tuibur habit had an increased risk of stomach cancer if they carried the GSTM1 null genotype and GSTT1 non-null genotype[47].

CagL is a pilus protein of *H. pylori* that interacts with host cellular α5β1 integrins through its arginine-glycine-aspartate (RGD) motif, guiding proper positioning of the T4SS and translocation of CagA[48]. Deletion or sequence variations of CagL significantly diminished the ability of *H. pylori* to induce secretion of interleukin (IL)-8 by the host cell[49]. In a primary study, prevalence of *H. pylori* infection in the study population was found to be 52.5%. Most of the isolates were CagL genopositive (86.6%), and all had the RGD motif in their amino acid sequences. D58 and K59 polymorphisms in CagL-genopositive strains were significantly higher in GC patients ($P < 0.05$). Combined D58K59 polymorphism was associated with a higher risk of GC (3.8-fold) when compared to NUD. It was concluded that *H. pylori* CagL amino acid polymorphisms, such as D58K59, are correlated with a higher risk of GC in the Indian population[50].

MOLECULAR PATHOGENESIS OF *H. PYLORI* INFECTION

CD4+ T helper cells (Th) are recognized as a key component of the adaptive immune response to extracellular bacteria and a dominant component of immune responses to *H. pylori*[51-53]. *H. pylori* evokes a weaker Th17 response, followed by a dominant and more persistent Th1 response that is paralleled by an immunoregulatory CD4+ T cell response characterized by T regulatory cells slowly accumulating at the beginning of the infection, reaching the highest level at 30 d post-infection which is sustained over time[54].

A close relationship between plasma malondialdehyde (MDA) and nitric oxide (NO) levels was found with gastric histopathology and genotypes of *H. pylori* in South India. Levels of MDA and NO were higher in subjects infected with genotype-1 of *H. pylori* than those with other genotypes suggesting more precise interaction of highly virulent strains of *H. pylori* in eliciting severe tissue damage[55]. Another study from South India reported that *H. pylori* infection may increase the expression of c-H-ras p21 early in the process of gastric carcinogenesis[56].

H. pylori infection has a negative effect on the MMR system, and the activity of various MMR proteins such as hMLH1, PMS1, PMS2, hMSH2 and hMSH6 is significantly reduced in the presence of *H. pylori* infection. An inverse relationship between microsatellite instability (MSI) and CagA protein has also been reported suggesting that other factors are also responsible for MSI in GC in addition to the bacterium CagA protein[57]. *H. pylori* induces genomic instability of (CA) n repeats in mice resulting in impairment of MMR machinery and generating a transient mutator phenotype making the gastric epithelia susceptible to aggregation of genetic instability leading to gastric carcinogenesis[58]. Some researchers contradict the above findings and suggest that both *H. pylori* negative and positive tumors showed the same amount of MSI in GC, and even after eradication of the bacterium there were no changes in chromosomal aberrations[59]. This suggested that *H. pylori* infection may act as a synergistic factor in GC, but not a direct factor causing carcinogenesis by altering gene expression.

A detailed characterization of a functionally unknown gene (*HP986*) which was detected in isolates from patients with peptic ulcer and gastric carcinoma was performed. Expression and purification of recombinant HP986 (rHP986) revealed a novel, approximately 29 kDa protein in biologically active form that was associated with significant levels of humoral immune response in diseased individuals ($P < 0.001$). In addition, it was reported that rHP986 induced significant levels of tumor necrosis factor (TNF)-α and IL-8 in cultured human macrophages concurrent with the translocation of nuclear transcription factor-κB (NF-κB). Furthermore, rHP986 induced apoptosis of cultured macrophages through a Fas mediated pathway. Dissection of the underlying signaling mechanism revealed that rHP986 induces both TNFR1 and Fas expression leading to apoptosis. These authors further demonstrated the interaction of HP986 with TNFR1 through computational and experimental approaches. Independent pro-inflammatory and apoptotic responses triggered by rHP986 may possibly work as a survival strategy to gain a niche through inflammation and to counter the activated macrophages to avoid clearance[60,61].

Analysis of the p53 codon 72 SNP in 372 biopsy samples from our center revealed that in the North Indian normal population the p53 Arg/Arg (40.59%) and Pro/Arg variant (33.66%) were higher as compared to the p53 Pro/Pro variant (25.75%). Gastritis and gastropathy had a similar distribution, whereas gastric cancer, GU and DU cases showed a decrease in the Arg/Arg variant and an increase in the Arg/Pro and Pro/Pro variant. It was also found that the presence of the p53 Pro allele along with a decrease in the Arg/Arg allele is associated with a small, but non-significant increase in the risk of gastric lesions, suggesting that p53 (Arg), is more effective in protecting stressed cells from neoplastic development than p53 (Pro). These findings are in accordance with Mantovani *et al*[62] and Bergamaschi *et al*[63]. We also found that the p53 (Arg) (Pro/Arg) variant is higher in normal

subjects. Variation in apoptotic index also correlated with a change in the pattern of the Arg/Arg allele in various diseases showing that this allele may prevent carcinogenic changes by stimulating apoptosis of damaged epithelial cells. This may be the reason for the low incidence of gastric cancer in North India despite a relatively higher incidence of *H. pylori* infection (Under Publication).

CONCLUSION

In conclusion, the Indian enigma is a variation in the prevalence of *H. pylori* infection and gastric cancer in different zones. The incidence of gastric cancer in the Indian continent cannot be attributed to infection by *H. pylori* only, other factors such as diet, tobacco and socio-economic status may also have a role.

REFERENCES

1 **Marshall BJ**, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* 1984; **1**: 1311-1315 [PMID: 6145023 DOI: 10.1016/S0140-6736(84)91816-6]

2 Schistosomes, liver flukes and Helicobacter pylori. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon, 7-14 June 1994. *IARC Monogr Eval Carcinog Risks Hum* 1994; **61**: 1-241 [PMID: 7715068]

3 **Deen NS**, Huang SJ, Gong L, Kwok T, Devenish RJ. The impact of autophagic processes on the intracellular fate of Helicobacter pylori: more tricks from an enigmatic pathogen? *Autophagy* 2013; **9**: 639-652 [PMID: 23396129 DOI: 10.4161/auto.23782]

4 **Wroblewski LE**, Peek RM, Wilson KT. Helicobacter pylori and gastric cancer: factors that modulate disease risk. *Clin Microbiol Rev* 2010; **23**: 713-739 [PMID: 20930071 DOI: 10.1128/CMR.00011-10]

5 **Goh KL**. Epidemiology of Helicobacter pylori infection in Malaysia--observations in a multiracial Asian population. *Med J Malaysia* 2009; **64**: 187-192 [PMID: 20527265]

6 **Hirai I**, Sasaki T, Kimoto A, Yamamoto Y, Azuma T, Mahachai V, Hansomburana P, Lertkupinit C, Luangjaru S, Noophan P, Chanatrirattanapan R, Piyanirandr V, Sappajit T, Suthivarakom K, Sangsuk L, Wangroongsarb P. Infection of less virulent Helicobacter pylori strains in asymptomatic healthy individuals in Thailand as a potential contributing factor to the Asian enigma. *Microbes Infect* 2010; **12**: 227-230 [PMID: 20036753 DOI: 10.1016/j.micinf.2009.12.007]

7 **Bhurgri Y**, Pervez S, Kayani N, Haider S, Ahmed R, Usman A, Bashir I, Bhurgri A, Hasan SH, Zaidi SM. Rising incidence of gastric malignancies in Karachi, 1995- 2002. *Asian Pac J Cancer Prev* 2009; **10**: 41-44 [PMID: 19469622]

8 **Graham DY**, Lu H, Yamaoka Y. African, Asian or Indian enigma, the East Asian Helicobacter pylori: facts or medical myths. *J Dig Dis* 2009; **10**: 77-84 [PMID: 19426388 DOI: 10.1111/j.1751-2980.2009.00368.x]

9 **Mohandas KM**, Nagral A. Epidemiology of digestive tract cancers in India. II. Stomach, and gastrointestinal lymphomas. *Indian J Gastroenterol* 1998; **17**: 24-27 [PMID: 9465510]

10 **Sharma A**, Radhakrishnan V. Gastric cancer in India. *Indian J Med Paediatr Oncol* 2011; **32**: 12-16 [PMID: 21731210 DOI: 10.4103/0971-5851.81884]

11 **Misra V**, Misra SP, Dwivedi M, Singh PA. Point prevalence of peptic ulcer and gastric histology in healthy Indians with Helicobacter pylori infection. *Am J Gastroenterol* 1997; **92**: 1487-1491 [PMID: 9317069]

12 **Dikshit RP**, Mathur G, Mhatre S, Yeole BB. Epidemiological review of gastric cancer in India. *Indian J Med Paediatr Oncol* 2011; **32**: 3-11 [PMID: 21731209 DOI: 10.4103/0971-5851.81883]

13 **Misra V,** Misra SP, Singh MK, Singh PA, Dwivedi M. Prevalence of H. pylori in patients with gastric cancer. *Indian J Pathol Microbiol* 2007; **50**: 702-707 [PMID: 18306532]

14 **Quigley EM**, Keohane J. Dyspepsia. *Curr Opin Gastroenterol* 2008; **24**: 692-697 [PMID: 19122517 DOI: 10.1097/MOG.0b013e328313b983]

15 **Malhotra SL**. Geographical distribution of gastrointestinal cancers in India with special reference to causation. *Gut* 1967; **8**: 361-372 [PMID: 6039725 DOI: 10.1136/gut.8.4.361]

16 **Katelaris PH,** Tippett GH, Norbu P, Lowe DG, Brennan R, Farthing MJ. Dyspepsia, Helicobacter pylori, and peptic ulcer in a randomly selected population in India. *Gut* 1992; **33**: 1462-1466 [PMID: 1452068]

17 **Yassibaş E**, Arslan P, Yalçin S. Evaluation of dietary and life-style habits of patients with gastric cancer: a case-control study in Turkey. *Asian Pac J Cancer Prev* 2012; **13**: 2291-2297 [PMID: 22901209 DOI: 10.7314/APJCP.2012.13.5.2291]

18 **Mathew A**, Gangadharan P, Varghese C, Nair MK. Diet and stomach cancer: a case-control study in South India. *Eur J Cancer Prev* 2000; **9**: 89-97 [PMID: 10830575 DOI: 10.1097/00008469-200004000-00004]

19 **Rao DN**, Ganesh B, Dinshaw KA, Mohandas KM. A case-control study of stomach cancer in Mumbai, India. *Int J Cancer* 2002; **99**: 727-731 [PMID: 12115507 DOI: 10.1002/ijc.10339]

20 **Wang XQ**, Terry PD, Yan H. Review of salt consumption and stomach cancer risk: epidemiological and biological evidence. *World J Gastroenterol* 2009; **15**: 2204-2213 [PMID: 19437559 DOI: 10.3748/wjg.15.2204]

21 **Phukan RK**, Narain K, Zomawia E, Hazarika NC, Mahanta J. Dietary habits and stomach cancer in Mizoram, India. *J Gastroenterol* 2006; **41**: 418-424 [PMID: 16799882 DOI: 10.1007/s00535-006-1761-x]

22 **Carroll RE**, Benya RV, Turgeon DK, Vareed S, Neuman M, Rodriguez L, Kakarala M, Carpenter PM, McLaren C, Meyskens FL, Brenner DE. Phase IIa clinical trial of curcumin for the prevention of colorectal neoplasia. *Cancer Prev Res* (Phila) 2011; **4**: 354-364 [PMID: 21372035 DOI: 10.1158/1940-6207.CAPR-10-0098]

23 **Kim DC**, Kim SH, Choi BH, Baek NI, Kim D, Kim MJ, Kim KT. Curcuma longa extract protects against gastric ulcers by blocking H2 histamine receptors. *Biol Pharm Bull* 2005; **28**: 2220-2224 [PMID: 16327153 DOI: 10.1248/bpb.28.2220]

24 **Fleischauer AT**, Arab L. Garlic and cancer: a critical review of the epidemiologic literature. *J Nutr* 2001; **131**: 1032S-1040S [PMID: 11238811]

25 **González CA**, Pera G, Agudo A, Bueno-de-Mesquita HB, Ceroti M, Boeing H, Schulz M, Del Giudice G, Plebani M, Carneiro F, Berrino F, Sacerdote C, Tumino R, Panico S, Berglund G, Simán H, Hallmans G, Stenling R, Martinez C, Dorronsoro M, Barricarte A, Navarro C, Quiros JR, Allen N, Key TJ, Bingham S, Day NE, Linseisen J, Nagel G, Overvad K, Jensen MK, Olsen A, Tjønneland A, Büchner FL, Peeters PH, Numans ME, Clavel-Chapelon F, Boutron-Ruault MC, Roukos D, Trichopoulou A, Psaltopoulou T, Lund E, Casagrande C, Slimani N, Jenab M, Riboli E. Fruit and vegetable intake and the risk of stomach and oesophagus adenocarcinoma in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST). *Int J Cancer* 2006; **118**: 2559-2566 [PMID: 16380980 DOI: 10.1002/ijc.21678]

26 **Sintara K**, Thong-Ngam D, Patumraj S, Klaikeaw N, Chatsuwan T. Curcumin suppresses gastric NF-kappaB activation and macromolecular leakage in Helicobacter pylori-infected rats. *World J Gastroenterol* 2010; **16**: 4039-4046 [PMID: 20731017 DOI: 10.3748/wjg.v16.i32.4039]

27 **Yadav SK**, Sah AK, Jha RK, Sah P, Shah DK. Turmeric (curcumin) remedies gastroprotective action. *Pharmacogn Rev* 2013; **7**: 42-46 [PMID: 23922455 DOI: 10.4103/0973-7847.112

843]
28 **Singh K**, Ghoshal UC. Causal role of Helicobacter pylori infection in gastric cancer: an Asian enigma. *World J Gastroenterol* 2006; **12**: 1346-1351 [PMID: 16552799]
29 **Mohandas KM**, Jagannath P. Epidemiology of digestive tract cancers in India. VI. Projected burden in the new millennium and the need for primary prevention. *Indian J Gastroenterol* 2000; **19**: 74-78 [PMID: 10812820]
30 **Tomb JF**, White O, Kerlavage AR, Clayton RA, Sutton GG, Fleischmann RD, Ketchum KA, Klenk HP, Gill S, Dougherty BA, Nelson K, Quackenbush J, Zhou L, Kirkness EF, Peterson S, Loftus B, Richardson D, Dodson R, Khalak HG, Glodek A, McKenney K, Fitzegerald LM, Lee N, Adams MD, Hickey EK, Berg DE, Gocayne JD, Utterback TR, Peterson JD, Kelley JM, Cotton MD, Weidman JM, Fujii C, Bowman C, Watthey L, Wallin E, Hayes WS, Borodovsky M, Karp PD, Smith HO, Fraser CM, Venter JC. The complete genome sequence of the gastric pathogen Helicobacter pylori. *Nature* 1997; **388**: 539-547 [PMID: 9252185 DOI: 10.1038/41483]
31 **Behrens W**, Bönig T, Suerbaum S, Josenhans C. Genome sequence of Helicobacter pylori hpEurope strain N6. *J Bacteriol* 2012; **194**: 3725-3726 [PMID: 22740658 DOI: 10.1128/JB.00386-12]
32 **Kumar N**, Mukhopadhyay AK, Patra R, De R, Baddam R, Shaik S, Alam J, Tiruvayipati S, Ahmed N. Next-generation sequencing and de novo assembly, genome organization, and comparative genomic analyses of the genomes of two Helicobacter pylori isolates from duodenal ulcer patients in India. *J Bacteriol* 2012; **194**: 5963-5964 [PMID: 23045484 DOI: 10.1128/JB.01371-12]
33 **Devi SM**, Ahmed I, Francalacci P, Hussain MA, Akhter Y, Alvi A, Sechi LA, Mégraud F, Ahmed N. Ancestral European roots of Helicobacter pylori in India. *BMC Genomics* 2007; **8**: 184 [PMID: 17584914 DOI: 10.1186/1471-2164-8-184]
34 **Cooke CL**, Huff JL, Solnick JV. The role of genome diversity and immune evasion in persistent infection with Helicobacter pylori. *FEMS Immunol Med Microbiol* 2005; **45**: 11-23 [PMID: 15949928 DOI: 10.1016/j.femsim.2005.04.002]
35 **Suerbaum S**, Smith JM, Bapumia K, Morelli G, Smith NH, Kunstmann E, Dyrek I, Achtman M. Free recombination within Helicobacter pylori. *Proc Natl Acad Sci USA* 1998; **95**: 12619-12624 [PMID: 9770535 DOI: 10.1073/pnas.95.21.12619]
36 **Israel DA**, Salama N, Krishna U, Rieger UM, Atherton JC, Falkow S, Peek RM. Helicobacter pylori genetic diversity within the gastric niche of a single human host. *Proc Natl Acad Sci USA* 2001; **98**: 14625-14630 [PMID: 11724955 DOI: 10.1073/pnas.251551698]
37 **Falush D**, Kraft C, Taylor NS, Correa P, Fox JG, Achtman M, Suerbaum S. Recombination and mutation during long-term gastric colonization by Helicobacter pylori: estimates of clock rates, recombination size, and minimal age. *Proc Natl Acad Sci USA* 2001; **98**: 15056-15061 [PMID: 11742075 DOI: 10.1073/pnas.251396098]
38 **Gill HH**, Desai HG, Majmudar P, Mehta PR, Prabhu SR. Epidemiology of Helicobacter pylori: the Indian scenario. *Indian J Gastroenterol* 1993; **12**: 9-11 [PMID: 8330925]
39 **Patra R**, Chattopadhyay S, De R, Ghosh P, Ganguly M, Chowdhury A, Ramamurthy T, Nair GB, Mukhopadhyay AK. Multiple infection and microdiversity among Helicobacter pylori isolates in a single host in India. *PLoS One* 2012; **7**: e43370 [PMID: 22952670 DOI: 10.1371/journal.pone.0043370]
40 **Jain A**, Buddhiraja S, Khurana B, Singhal R, Nair D, Arora P, Gangwal P, Mishra SK, Uppal B, Gondal R, Kar P. Risk factors for duodenal ulcer in north India. *Trop Gastroenterol* 1999; **20**: 36-39 [PMID: 10464447]
41 **Jain AK**, Dayal VM. Helicobacter pylori recolonization and ulcer relapse after its eradication in India. *Indian J Gastroenterol* 1997; **16** Suppl 1: S22-S24 [PMID: 9465499]
42 **Misra V**, Bisht D, Misra SP, Dwivedi M, Bhatia R. Argyrophilic nucleolar organizer regions in Helicobacter pylori-associated gastric lesions. *APMIS* 2000; **108**: 448-452 [PMID: 11028808]
43 **Singh V**, Trikha B, Nain CK, Singh K, Vaiphei K. Epidemiology of Helicobacter pylori and peptic ulcer in India. *J Gastroenterol Hepatol* 2002; **17**: 659-665 [PMID: 12100610 DOI: 10.1046/j.1440-1746.2002.02746.x]
44 **Tovey FI**, Hobsley M, Kaushik SP, Pandey R, Kurian G, Singh K, Sood A, Jehangir E. Duodenal gastric metaplasia and Helicobacter pylori infection in high and low duodenal ulcer-prevalent areas in India. *J Gastroenterol Hepatol* 2004; **19**: 497-505 [PMID: 15086592]
45 **Ghoshal U**, Kumar S, Jaiswal V, Tripathi S, Mittal B, Ghoshal UC. Association of microsomal epoxide hydrolase exon 3 Tyr113His and exon 4 His139Arg polymorphisms with gastric cancer in India. *Indian J Gastroenterol* 2013; **32**: 246-252 [PMID: 23580125 DOI: 10.1007/s12664-013-0332-3]
46 **Ghoshal U**, Tripathi S, Kumar S, Mittal B, Chourasia D, Kumari N, Krishnani N, Ghoshal UC. Genetic polymorphism of cytochrome P450 (CYP) 1A1, CYP1A2, and CYP2E1 genes modulate susceptibility to gastric cancer in patients with Helicobacter pylori infection. *Gastric Cancer* 2013 May 19; Epub ahead of print [PMID: 23686565 DOI: 10.1007/s10120-013-0269-3]
47 **Saxena A**, Shukla SK, Prasad KN, Ghoshal UC. Analysis of p53, K-ras gene mutation & Helicobacter pylori infection in patients with gastric cancer & peptic ulcer disease at a tertiary care hospital in north India. *Indian J Med Res* 2012; **136**: 664-670 [PMID: 23168708]
48 **Malakar M**, Devi KR, Phukan RK, Kaur T, Deka M, Puia L, Barua D, Mahanta J, Narain K. Genetic polymorphism of glutathione S-transferases M1 and T1, tobacco habits and risk of stomach cancer in Mizoram, India. *Asian Pac J Cancer Prev* 2012; **13**: 4725-4732 [PMID: 23167410 DOI: 10.7314/APJCP.2012.13.9.4725]
49 **Conradi J**, Tegtmeyer N, Woźna M, Wissbrock M, Michalek C, Gagell C, Cover TL, Frank R, Sewald N, Backert S. An RGD helper sequence in CagL of Helicobacter pylori assists in interactions with integrins and injection of CagA. *Front Cell Infect Microbiol* 2012; **2**: 70 [PMID: 22919661 DOI: 10.3389/fcimb.2012.00070]
50 **Backert S**, Clyne M, Tegtmeyer N. Molecular mechanisms of gastric epithelial cell adhesion and injection of CagA by Helicobacter pylori. *Cell Commun Signal* 2011; **9**: 28 [PMID: 22044679 DOI: 10.1186/1478-811X-9-28]
51 **Shukla SK**, Prasad KN, Tripathi A, Jaiswal V, Khatoon J, Ghsohal UC, Krishnani N, Husain N. Helicobacter pylori cagL amino acid polymorphisms and its association with gastroduodenal diseases. *Gastric Cancer* 2013; **16**: 435-439 [PMID: 22941498 DOI: 10.1007/s10120-012-0189-7]
52 **Hitzler I**, Kohler E, Engler DB, Yazgan AS, Müller A. The role of Th cell subsets in the control of Helicobacter infections and in T cell-driven gastric immunopathology. *Front Immunol* 2012; **3**: 142 [PMID: 22675328 DOI: 10.3389/fimmu.2012.00142]
53 **Bamford KB**, Fan X, Crowe SE, Leary JF, Gourley WK, Luthra GK, Brooks EG, Graham DY, Reyes VE, Ernst PB. Lymphocytes in the human gastric mucosa during Helicobacter pylori have a T helper cell 1 phenotype. *Gastroenterology* 1998; **114**: 482-492 [PMID: 9496938 DOI: 10.1016/S0016-5085(98)70531-1]
54 **Smythies LE**, Waites KB, Lindsey JR, Harris PR, Ghiara P, Smith PD. Helicobacter pylori-induced mucosal inflammation is Th1 mediated and exacerbated in IL-4, but not IFN-gamma, gene-deficient mice. *J Immunol* 2000; **165**: 1022-1029 [PMID: 10878379]
55 **Carbo A**, Bassaganya-Riera J, Pedragosa M, Viladomiu M, Marathe M, Eubank S, Wendelsdorf K, Bisset K, Hoops S, Deng X, Alam M, Kronsteiner B, Mei Y, Hontecillas R. Pre-

dictive computational modeling of the mucosal immune responses during Helicobacter pylori infection. *PLoS One* 2013; **8**: e73365 [PMID: 24039925 DOI: 10.1371/journal.pone.0073365]

56 **Tiwari SK**, Manoj G, Sharma V, Sivaram G, Saikant R, Bardia A, Sharma VK, Abid Z, Khan AA, Habeeb MA, Habibullah CM, Kumar BS, Nandan A. Relevance of Helicobacter pylori genotypes in gastric pathology and its association with plasma malondialdehyde and nitric oxide levels. *Inflammopharmacology* 2010; **18**: 59-64 [PMID: 20143166 DOI: 10.1007/s10787-010-0031-y]

57 **Sureka C**, Ramesh T. Molecular assessment of c-H-ras p21 expression in Helicobacter pylori-mediated gastric carcinogenesis. *Mol Cell Biochem* 2012; **362**: 169-176 [PMID: 22045063 DOI: 10.1007/s11010-011-1139-0]

58 **Ferrasi AC**, Pinheiro NA, Rabenhorst SH, Caballero OL, Rodrigues MA, de Carvalho F, Leite CV, Ferreira MV, Barros MA, Pardini MI. Helicobacter pylori and EBV in gastric carcinomas: methylation status and microsatellite instability. *World J Gastroenterol* 2010; **16**: 312-319 [PMID: 20082476]

59 **Meira LB**, Bugni JM, Green SL, Lee CW, Pang B, Borenshtein D, Rickman BH, Rogers AB, Moroski-Erkul CA, McFaline JL, Schauer DB, Dedon PC, Fox JG, Samson LD. DNA damage induced by chronic inflammation contributes to colon carcinogenesis in mice. *J Clin Invest* 2008; **118**: 2516-2525 [PMID: 18521188 DOI: 10.1172/JCI35073]

60 **Ohara T**, Kasanuki J, Ohara H, Kanoh Y, Suzuki H, Hashimoto H, Chiba T, Morishita T, Hibi T. Analysis of the differences in structural chromosomal aberrations of the gastric mucosa between H. pylori positive and negative gastric cancer patients: involvement of H. pylori in the onset of gastric cancer and examination of the mechanism in gastric carcinogenesis following H. pylori eradication. *Oncol Rep* 2006; **16**: 1333-1342 [PMID: 17089058]

61 **Alvi A**, Ansari SA, Ehtesham NZ, Rizwan M, Devi S, Sechi LA, Qureshi IA, Hasnain SE, Ahmed N. Concurrent proinflammatory and apoptotic activity of a Helicobacter pylori protein (HP986) points to its role in chronic persistence. *PLoS One* 2011; **6**: e22530 [PMID: 21789261 DOI: 10.1371/journal.pone.0022530]

62 **Mantovani F**, Tocco F, Girardini J, Smith P, Gasco M, Lu X, Crook T, Del Sal G. The prolyl isomerase Pin1 orchestrates p53 acetylation and dissociation from the apoptosis inhibitor iASPP. *Nat Struct Mol Biol* 2007; **14**: 912-920 [PMID: 17906639]

63 **Bergamaschi D**, Samuels Y, Sullivan A, Zvelebil M, Breyssens H, Bisso A, Del Sal G, Syed N, Smith P, Gasco M, Crook T, Lu X. iASPP preferentially binds p53 proline-rich region and modulates apoptotic function of codon 72-polymorphic p53. *Nat Genet* 2006; **38**: 1133-1141 [PMID: 16964264]

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