World Journal of Gastrointestinal Oncology

Online Submissions: http://www.wjgnet.com/1948-5204office
wjgo@wjgnet.com
doi:10.4251/wjgo.v2.i6.265

World J Gastrointest Oncol 2010 June 15; 2(6): 265-271
ISSN 1948-5204 (online)
© 2010 Baishideng. All rights reserved.

TOPIC HIGHLIGHT

Angelo Zullo, MD, *Series Editor*

Role of interleukin polymorphisms in gastric cancer: "Pros and cons"

Francesco Perri, Fulvia Terracciano, Marco Gentile, Antonio Merla, Daniela Scimeca, Angelo Zullo

Francesco Perri, Fulvia Terracciano, Marco Gentile, Antonio Merla, Daniela Scimeca, Department of Gastroenterology and Digestive Endoscopy, "Casa Sollievo della Sofferenza" Hospital, IRCCS, 71013 San Giovanni Rotondo (FG), Italy
Angelo Zullo, Department of Gastroenterology and Digestive Endoscopy, "Nuovo Regina Margherita" Hospital, 00153 Rome, Italy
Author contributions: All of the authors equally contributed to this paper.
Correspondence to: Dr. Francesco Perri, Department of Gastroenterology and Digestive Endoscopy, "Casa Sollievo della Sofferenza" Hospital, IRCCS, V.le Cappuccini, 71013 San Giovanni Rotondo (FG), Italy. fp.perri@libero.it
Telephone: +39-882-410235 Fax: +39-0882-410784
Received: November 10, 2009 Revised: December 8, 2009
Accepted: December 15, 2009
Published online: June 15, 2010

Abstract

Helicobacter pylori (*H. pylori*) infection is the leading cause of gastric cancer worldwide. Infection with this bacterium causes a chronic active immune response that persists for the life of the host. The combination of bacterial factors, environmental insults, and the host immune response drives the initiation and progression of mucosal atrophy, metaplasia, and dysplasia toward GC. Among the host factors, IL-1 gene cluster polymorphisms (IL-1B encoding IL-1β and IL-1RN encoding IL-1ra, its naturally occurring receptor antagonist) play a decisive role in modulating the risk of developing hypochlorhydria, gastric atrophy and GC in the presence of *H. pylori* infection. In particular, one single nucleotide polymorphism in the IL-1B promoter (IL-1B-511C/T), and the short allele of a 86-bp variable number of tandem repeats polymorphism in the IL-1RN second intron (IL-1RN*2) are associated with an increased risk for GC. However this hypothesis is still to be fully confirmed. This review focuses on the divergent results obtained by several epidemiological and functional *in vitro* and *in vivo* studies and show that IL-1 genotyping has still no role in the clinical management of patients with *H. pylori* infection.

© 2010 Baishideng. All rights reserved.

Key words: Cytokine; Gastric cancer; Gene; Interleukin; Helicobacter pylori; Polymorphism

Peer reviewer: Yukinori Kurokawa, MD, PhD, Department of Surgery, Osaka National Hospital, 2-1-14, Hoenzaka, Chuo-ku, Osaka 540-0006, Japan

Perri F, Terracciano F, Gentile M, Merla A, Scimeca D, Zullo A. Role of interleukin polymorphisms in gastric cancer: "Pros and cons". *World J Gastrointest Oncol* 2010; 2(6): 265-271 Available from: URL: http://www.wjgnet.com/1948-5204/full/v2/i6/265.htm DOI: http://dx.doi.org/10.4251/wjgo.v2.i6.265

INTRODUCTION

Gastric cancer (GC) is the fourth most common cancer in the world, behind only cancers of the lung, colon, and breast, and the second leading cause of cancer death with an estimated 700000 deaths annually[1]. There are marked geographic variations in GC incidence, with the highest rates in Japan, China and South America and much lower rates in Western countries, including the USA[2]. The overwhelming majority (i.e. 90%-95%) of GCs are adenocarcinomas with non-Hodgkin's lymphomas and stromal tumors comprising the remainder. There are two main types of gastric adenocarcinoma: intestinal and diffuse[3]. These types differ in their histology, epidemiology, pathogenesis, genetic profile, and clinical outcome[4]. The intestinal-type is characterized by the formation of gland-like structures and is linked closely to environmental and dietary risk factors such as *Helicobacter pylori* (*H. pylori*) infection, tobacco smoking, low consumption of fresh fruit and vegetables, and high intake of red meat, salt, and unrefrigerated food. The

accepted paradigm for the pathogenesis of the intestinal-type is a multistep progression from chronic gastritis to gastric atrophy, intestinal metaplasia, and dysplasia[5-7]. The diffuse-type is generally less common, and is found with the same frequency throughout the world. The histology of the diffuse-type is poorly differentiated and lacks glandular structures. Patients with the diffuse-type typically are younger and have a worse prognosis than those with the intestinal type. The pathogenesis of diffuse-type GC is poorly understood, although *H. pylori* infection is also a predisposing factor[8]. There are no known histological precursor lesions of this type of GC[4].

GC AND *H. PYLORI* INFECTION

Since the initial description of *H. pylori* by Marshall and Warren in 1984[9], several studies have been performed to evaluate the role of *H. pylori* infection in GC. In 1994, the International Agency for Research on Cancer classified *H. pylori* as a class I carcinogen[10] on the basis of epidemiologic data and animal models of the infection[11-13]. It has been estimated that almost 80% of GCs are the end result of a long-standing *H. pylori*-associated chronic active gastritis[14,15] and programmes of mass eradication of the bacterium have been proposed especially for populations at high risk of GC.

H. pylori infection is the most common chronic infection in humans affecting almost half of the world's population. Although infection with *H. pylori* almost always results in chronic active gastritis, only a fraction of those infected (approximately 15%) will develop gastric or duodenal ulcer disease and a minority (less than 1%) will develop GC[16,17]. The risk of GC is highest in patients with atrophy, corpus-predominant gastritis and intestinal metaplasia, further supporting the hypothesis that these lesions represent premalignant mucosal changes. There is also an increased risk of GC in infected patients with non-ulcer dyspepsia, and gastric ulcer, but not in those with duodenal ulcer. The extremely variable natural history of *H. pylori*-associated chronic gastritis remains unexplained. Predisposition to *H. pylori*-associated GC is most likely multifactorial, including the interaction of bacterial, host, and environmental factors. The role of environmental factors other than *H. pylori* infection has been extensively reviewed elsewhere[18-22], and it will not be considered here.

The role of host genetics is suggested by family studies showing that first-degree relatives of patients with GC have a two- to three-fold increased risk of developing GC which can be only in part ascribed to either familial clustering of *H. pylori* infection or similar exposure to environmental and food carcinogens. Host genetic polymorphisms have emerged in recent years as important determinants of *H. pylori*-induced GC. In particular, pro-inflammatory cytokine gene polymorphisms have been extensively studied because they seem to influence the severity and the extent of gastric inflammation due to *H. pylori* infection and contribute to GC initiation and progression.

The role of host immune response is supported by the finding that a robust Th1 immune response by the host in reaction to *H. pylori* infection is correlated positively with GC risk[23]. Recent studies have shown that polymorphic genes of the innate immune response specifically involved in handling the *H. pylori* attack are also implicated in gastric carcinogenesis[24]. Finally, the role of virulence factors of *H. pylori* (the best studied are CagA and VacA) is shown by the fact that CagA and VacA producing strains are reported to be related to more severe clinical outcome and to GC in particular[25-29].

In the present review, we have focused our attention on the role of pro-inflammatory cytokine gene polymorphisms in gastric carcinogenesis and show that their contribution in the initiation of GC is still some way from being fully elucidated.

PRO-INFLAMMATORY CYTOKINE GENE POLYMORPHISMS AND GC: PROs

H. pylori infection is associated with divergent clinical outcomes which range from simple asymptomatic gastritis to more serious clinical conditions such as ulcer disease or GC. The determinants of these outcomes are mainly represented by the severity and distribution of the *H. pylori* induced gastritis. Three phenotypes of gastritis have been described which correlate closely with the clinical outcome of *H. pylori* infection. The first phenotype which is called the "simple mild gastritis" phenotype, is characterized by mild pangastritis with little interference on gastric acid secretion. This phenotype is generally found in asymptomatic subjects who develop no serious gastrointestinal disease. The second phenotype is the so-called "duodenal ulcer" phenotype and is characterized by an antral-predominant pattern of gastritis with relative sparing of the acid producing corpus mucosa. Subjects with this phenotype have severe antral inflammation, high gastrin, relatively healthy corpus mucosa, and very high acid output. These subjects have also a defective inhibitory control of gastric acid secretion with low antral somatostatin levels. These pathophysiologic abnormalities in predisposed individuals contribute to the development of peptic ulcers, particularly duodenal and pre-pyloric ulcers. The third and most serious phenotype is the "GC phenotype" which is characterized by a corpus-predominant gastritis, multifocal gastric atrophy, and hypo- or achlorhydria. El-Omar *et al*[30,31] have shown that proinflammatory IL-1 gene cluster polymorphisms (IL-1B encoding IL-1β and IL-1RN encoding IL-1ra, its naturally occurring receptor antagonist) increase the risk of developing hypochlorhydria and gastric atrophy in response to *H. pylori* infection. This risk also extends to GC itself with a 2- to 3-fold increased risk of malignancy compared with subjects who have the less pro-inflammatory genotypes. Pro-inflammatory IL-1 genotypes increase the risk of both intestinal and diffuse types of GC, but the risk is restricted to the noncardia site. The IL-1B gene encoding IL-1β has two diallelic polymorphisms in the promoter region at positions -511 and -31, representing C-T and T-C transitions, respectively, in near total linkage disequilibrium[30,32,33]. The less common alleles of these

loci (IL-1B-511T and IL-1B-31C) have been found to be associated with GC[30,34-36]. It has been hypothesized that *H. pylori* infected patients carrying either the IL-1B-511T or the IL-1B-31C allele have increased gastric mucosal levels of IL-1β. This leads to a sustained suppression of acid secretion and induces a vigorous inflammatory response which extends from the antrum to the corpus mucosa[30,37]. As the inflammatory process extends across the corpus, acid secretion is further inhibited in a continuing process that accelerates glandular loss, onset of gastric atrophy and, possibly, development of GC[30,37]. Another cytokine that has an important influence on IL-1β levels is IL-1ra, whose gene (IL-1RN) is also known to be polymorphic. The IL-1RN gene has a penta-allelic 86-base pair (bp) tandem repeat polymorphism [variable number of tandem repeat (VNTR)] in intron 2[38], the less common of which, the IL-1RN*2, has been associated with GC[30].

Individuals with the IL-1B-31*C or -511*T and IL-1RN*2/*2 genotypes are thought to be at increased risk of developing hypochlorhydria and gastric atrophy in response to *H. pylori* infection. Indeed, the IL-1 markers have no effect on risk of cardia gastric adenocarcinoma and esophageal adenocarcinoma.

The association between IL-1 gene cluster polymorphisms and GC and its precursors has been confirmed independently by other groups covering white, Asian, and Hispanic populations[34-37,39-42]. Indirect evidence of the role of IL-1 in *H. pylori*-induced gastric carcinogenesis comes from a transgenic mouse model in which IL-1 overproduction leads to stepwise spontaneous inflammation, dysplasia, and carcinoma of the stomach through an activation of the IL-1B/NF-κB pathway in myeloid-derived suppressor cells[43]. Significantly, these IL-1 transgenic mice proceed through a multistage process that mimics human gastric neoplasia. These changes occur even in the absence of *H. pylori* infection which, when introduced, leads to an acceleration of these abnormalities.

Single-nucleotide polymorphisms (SNPs) in several other genes such as tumour necrosis factor (TNF)[31,36,44,45], IL-8[46,47], HLA-DQB1[48] and IL-12[49,50] and in genes encoding the anti-inflammatory cytokines IL-10[31,45,50,51] and IL-4[51] have been associated with GC risk with controversial results. Of note, carriage of multiple SNPs in IL-1B, IL1-RN, IL-10 and TNF seems to exert a synergistic increase in risk of GC when *H. pylori* infection is present[31,35,36].

PRO-INFLAMMATORY CYTOKINE GENE POLYMORPHISMS AND GC: CONs

Although the hypothesis of a pathogenic link between pro-inflammatory cytokine gene polymorphism and gastric carcinogenesis induced by *H. pylori* infection is fascinating, some questions are still unanswered. First of all, the functional effects of these polymorphisms on *in vitro* IL-1β and IL-1ra production[32,52-55] are not clear. For example, it has been reported that *Mycobacterium tuberculosis*-stimulated IL-1β induction from mononuclear cells of carriers of the IL1B-511 T allele was slightly higher, but in a statistically non significant way, than those of the C allele[56]. No association between polymorphism on IL-1B31 (and IL-1B511) and IL-1β production was found using whole blood of healthy individuals stimulated with *Escherichia coli* lipopolysaccharide[57]. In one study, the IL-1RN*2 allele (but not the IL-1B511 allele) was found to be associated with an increased production of IL-1β protein in monocytes stimulated with a combination of phorbol ester and calcium ionophore[54]. In another study, however, the IL-1RN*2 allele was associated with an increased production of IL-1ra protein without a significant effect on IL-1β secretion in monocytes stimulated with GM-CSF[55].

Studies performed in human subjects have not contributed to elucidation of the problem. In fact, gastric mucosal levels of IL-1β and IL-1ra can be affected by several factors other than IL-1B and IL-1RN genotypes, such as the presence of inflammation and atrophy at the sites of biopsy sampling (antrum or fundus) in the stomach, the *H. pylori* density, the age of patients, and the disease presentation. Nevertheless, gastric mucosal IL-1β levels have been measured in *H. pylori* infected patients with variant IL-1B-511 and IL-1RN genotypes. In one study, carriers of the IL-1B-511T/T genotype or the IL-1RN*2 allele had higher mucosal IL-1β levels than noncarriers[53]. In another study, *H. pylori* infected individuals with the IL-1B-511 T/T genotype had higher gastric pH, lower pepsinogen I /pepsinogen II ratios, higher gastric atrophy and gastritis scores compared with those of C/T and C/C genotypes[58]. However, these findings could not be completely confirmed by other authors. In a Chinese study, subjects with *H. pylori* infection had IL-1β mucosal levels significantly higher than non infected subjects, but this was irrespective of IL-1B genotype[59]. However, when only GC patients were considered, IL-1β levels were significantly higher in subjects with the IL-1B-31 T/T genotype compared to IL-1B-31C/T and C/C genotypes. As a consequence of the strong linkage disequilibrium existing between the IL-1B-31 and IL-1B-511 alleles, this finding implies that Chinese GC patients with the IL-1B-511 C/C genotype have IL-1β levels significantly higher than those with the IL-1B-511 C/T and T/T genotypes. The same conclusion was obtained in another study from Japanese researchers who found that IL-1B31 T/T and IL-1B-511 C/C genotypes were associated with an increased IL-1β production in the gastric body[60]. Surprisingly, these results are the reverse of those obtained in Western populations in which the highest IL-1β levels are found in subjects with IL-1B-511 T/T genotypes. Up to now, there is no clear explanation why the IL-1B-511 T allele (or the IL-1B 31C allele) regulates IL-1β expression in a different way in Western and Eastern populations. Finally, other reports from Asian countries were unable to find any differences in basal and maximal acid output among the three IL-1B-511 genotypes[61].

An interesting study performed in Italy showed that patients with atrophic body gastritis (ABG) showed a similar distribution of proinflammatory and wild-type alleles of IL-1B-511 and IL-1RN polymorphisms compared to

Table 1 Odd ratios, 95% confidence interval and number of studies of IL1B–511 and IL-1RN 86bp VTNR genotypes associated with GC[67,75]

	Studies	Cases	Controls	Odd ratio	95% CI
IL1B–511					
All populations	38	7118	8326	1.10*	1.02-1.18
Caucasians	17	2114	2890	1.29*	1.15-1.46
Asians	21	4414	4958	0.97	0.88-1.07
IL-1RN-86bp VTNR					
All populations	34	5602	7950	1.19*	1.09-1.30
Caucasians	9	1494	2216	1.33*	1.17-1.52
Asians	16	3109	3872	1.00	0.86-1.18

*P-value < 0.05. GC: Gastric cancer.

age- and gender-matched controls. More interestingly, the IL-1 polymorphisms were associated neither with specific clinical, biochemical or histological features nor with the development of GC at long-term follow-up[62]. These findings have been confirmed in a dyspeptic population in Costa Rica, in which the IL-1RN polymorphisms were not associated with ABG[63]. Similar results were also found in a Portuguese population in which the pro-inflammatory IL-1 polymorphisms (i.e. the IL-1B-511*T or the IL-1RN*2) were associated with an increased risk of GC but not of ABG[36].

The role of IL-1 markers in GC has been extensively reviewed by means of meta-analyses. So far, three meta-analyses have been published to address this question with conflicting results, further confusing the issue[64-66]. Indeed, 2 of these concluded that the IL-1 proinflammatory genotypes increase the risk of GC[64,65] whilst the remainder failed to confirm such a finding[66]. A possible explanation of these divergent results is the different ethnicity of populations examined. A recent study reviewed in depth 203 relevant studies assessing 225 polymorphisms across 95 genes significantly associated with GC[67]. All genotypes were considered by taking into account all studies together, and then grouping these studies according to the ethnicity of studied population, i.e. Asians and Caucasians. When the IL1B-511 polymorphism was analysed, the odd ratio (OR) for GC in individuals bearing the T allele (i.e. T/T and C/T genotypes) was respectively 1.10 (all populations) 1.29 (Caucasians) and 0.97 (Asians) (Table 1). Noteworthy, among 38 studies examined, only 5 showed a significant association between the T allele and GC; 4 studies published by 2 European research groups[30,34,35], 1 US[31], and the other published by Chinese researchers[41]. All the other 33 studies were unable to demonstrate a significant association between the IL1B-511 polymorphism and GC risk.

When the IL-1RN polymorphism was analysed, the risk for GC in individuals bearing at least one IL-1RN*2 allele (i.e. *2/*2 and *2/L genotypes) were respectively 1.19 (all populations), 1.33 (Caucasians), and 1.00 (Asians) (Table 1). Similarly as the IL1B-511 polymorphism, of 34 studies examined only 8 showed a significant association between the IL-1RN*2 allele and GC risk; 6 studies published by 3 European[30,40,68], 1 US[31], 1 Arab[69] and 1 Latin American[70] research groups and the other 2 published by 2 Chinese groups[71,72]. All the other 26 studies failed to demonstrate a significant association between the IL-1RN*2 allele and GC risk.

Other pro-inflammatory cytokine gene polymorphisms have been studied but their role in gastric carcinogenesis is less relevant than that postulated for IL-1B and IL1-RN genes.

CONCLUSION

The research on the role of interleukin polymorphisms in GC is still evolving with both "positive" studies which support and "null" studies which deny their contribution in gastric carcinogenesis. Why does this heterogeneity exist among these studies? The results for GC association studies are similar to findings for other complex diseases in which many early findings are not supported by subsequent studies. Failure to replicate results may arise from many causes[73] and not necessarily bring researchers to reject pathogenic hypotheses. Functional *in vitro* studies could partly overcome these problems by clarifying the biological plausibility of gene association studies. Another possibility is to shift from gene association studies to a gene-based approach in which all common variations within a candidate gene are considered jointly[74]. It is likely that improvement in study methodology may improve reliability of results and lead to a better understanding of the mechanisms promoting carcinogenesis.

In conclusion, we would pose the following question: what is the true impact of these gene polymorphisms on GC risk at population level? Would it be desirable to genotype healthy *H. pylori* infected individuals in order to identify those at greatest risk for GC? We believe that more information on the biological relevance of these polymorphisms in human cancer, in general, and GC, in particular, is needed. A recent study collected 161 meta-analyses and pooled analyses encompassing 18 cancer sites, 99 genes, and 344 gene-variant cancer associations[75]. The summary odds ratios for statistically significant associations ($P < 0.05$) were evaluated by estimating the false-positive report probability (FPRP) at a given prior probability and statistical power. The FPRP was calculated from the statistical power of the test (i.e. power to detect an OR of 1.5 or an OR of 1.2), the observed P-value, and a given prior probability (i.e. 0.001 and 0.000001) for the association[76]. The FPRP was calcu-

Table 2 Noteworthy gene-variant cancer associations with False-Positive Report Probabilities < 0.2 at a prior probability levels of 0.001 and 0.000001 to detect an OR of 1.5[75]

Gene	Variant	Comparison	FPRF at 0.001 (OR of 1.5)	FPRP at 0.000001 (OR of 1.5)	Cancer
CASP8	Asp302His	GC *vs* GG	0.028[a]	0.967	Breast
CHEK2	1100delC	Het *vs* NC	0.004[a]	0.782	Breast
TGFB1	Leu10Pro	TT *vs* CC	0.090[a]	0.990	Breast
GSTT1	Null	Null *vs* pres	0.074[a]	0.988	Colorectal
GSTM1	Null	Null *vs* pres	< 0.001[a]	< 0.001[a]	Bladder
NAT2	Acetylator	S *vs* I + R	< 0.001[a]	0.163[a]	Bladder
MTHFR	C677T	TT *vs* CT-CC	< 0.001[a]	0.140[a]	Stomach[a]
MDM2	SNP309	GG *vs* TT	0.162[a]	0.995	Lung
XPD	Lys751Gln	CC *vs* AA	0.143[a]	0.994	Lung
XRCC1	Arg399Gln	AA *vs* GG	0.038[a]	0.975	Lung
RNASEL	Asp541Glu	GT + GG *vs* TT	0.162[a]	0.995	Prostate
GSTM1	Null	Null *vs* pres	< 0.001[a]	< 0.001[a]	Leukaemia
GSTT1	Null	Null *vs* pres	0.023[a]	0.960	Leukaemia

[a]There is a noteworthy association at an FPRP level of 0.2.

lated for 2 levels of prior probability which are considered appropriate for a range of hypotheses; from a low probability (i.e. $P < 0.001$) appropriate for polymorphisms with known functional consequences in candidate genes, to a very low probability (i.e. $P < 0.000001$), appropriate for randomly selected variants as used in genome-wide association studies. Gene-variant cancer associations with a FPRP < 0.2 were considered noteworthy. There were 98 (98/344, 28%) statistically significant ($P < 0.05$) gene-variant cancer associations, of which 13 were considered noteworthy at a prior probability level of 0.001 and statistical power to detect an OR of 1.5 (Table 2). Of them, 4 remained noteworthy at a prior probability level of 0.000001 and statistical power to detect an OR of 1.5 (Table 2). The majority of the most noteworthy associations identified, however, were not polymorphisms but deletions with loss of gene function. In relation to GC, only the polymorphism 677 C > T of the methylenetetrahydrofolate reductase (MTHFR) gene, involved in folate metabolism, was found to have a noteworthy association with the disease. This polymorphism, however, is not directly implicated in *H. pylori* mucosal damage but is essential in modulating genomic DNA methylation thus regulating the expression of oncogenes and suppressor genes. The finding that *H. pylori* is able, by itself, to induce epigenetic changes even in normal mucosa of infected individuals[77] sheds new light on the pathogenesis of GC and indicate future direction for basic research.

REFERENCES

1 **Parkin DM**, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; **55**: 74-108
2 **Parkin DM**, Läärä E, Muir CS. Estimates of the worldwide frequency of sixteen major cancers in 1980. *Int J Cancer* 1988; **41**: 184-197
3 **Lauren P**. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. an attempt at a histo-clinical classification. *Acta Pathol Microbiol Scand* 1965; **64**: 31-49
4 **Nardone G**. Review article: molecular basis of gastric carcinogenesis. *Aliment Pharmacol Ther* 2003; **17** Suppl 2: 75-81
5 **Laurén PA**, Nevalainen TJ. Epidemiology of intestinal and diffuse types of gastric carcinoma. A time-trend study in Finland with comparison between studies from high- and low-risk areas. *Cancer* 1993; **71**: 2926-2933
6 **Houghton J**, Wang TC. Helicobacter pylori and gastric cancer: a new paradigm for inflammation-associated epithelial cancers. *Gastroenterology* 2005; **128**: 1567-1578
7 **Correa P**. Helicobacter pylori and gastric carcinogenesis. *Am J Surg Pathol* 1995; **19** Suppl 1: S37-S43
8 **Nardone G**, Rocco A, Malfertheiner P. Review article: helicobacter pylori and molecular events in precancerous gastric lesions. *Aliment Pharmacol Ther* 2004; **20**: 261-270
9 **Marshall BJ**, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* 1984; **1**: 1311-1315
10 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
11 **Nomura A**, Stemmermann GN, Chyou PH, Kato I, Perez-Perez GI, Blaser MJ. Helicobacter pylori infection and gastric carcinoma among Japanese Americans in Hawaii. *N Engl J Med* 1991; **325**: 1132-1136
12 An international association between Helicobacter pylori infection and gastric cancer. The EUROGAST Study Group. *Lancet* 1993; **341**: 1359-1362
13 **Watanabe T**, Tada M, Nagai H, Sasaki S, Nakao M. Helicobacter pylori infection induces gastric cancer in mongolian gerbils. *Gastroenterology* 1998; **115**: 642-648
14 **Uemura N**, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, Taniyama K, Sasaki N, Schlemper RJ. Helicobacter pylori infection and the development of gastric cancer. *N Engl J Med* 2001; **345**: 784-789
15 **Hohenberger P**, Gretschel S. Gastric cancer. *Lancet* 2003; **362**: 305-315
16 **Kuipers EJ**, Uyterlinde AM, Peña AS, Roosendaal R, Pals G, Nelis GF, Festen HP, Meuwissen SG. Long-term sequelae of Helicobacter pylori gastritis. *Lancet* 1995; **345**: 1525-1528
17 **Go MF**. Review article: natural history and epidemiology of Helicobacter pylori infection. *Aliment Pharmacol Ther* 2002; **16** Suppl 1: 3-15
18 **Ji BT**, Chow WH, Yang G, McLaughlin JK, Zheng W, Shu XO, Jin F, Gao RN, Gao YT, Fraumeni JF Jr. Dietary habits and stomach cancer in Shanghai, China. *Int J Cancer* 1998; **76**: 659-664
19 **Ramón JM**, Serra L, Cerdó C, Oromí J. Dietary factors and gastric cancer risk. A case-control study in Spain. *Cancer* 1993; **71**: 1731-1735
20 **Nazario CM**, Szklo M, Diamond E, Román-Franco A, Climent

C, Suarez E, Conde JG. Salt and gastric cancer: a case-control study in Puerto Rico. *Int J Epidemiol* 1993; **22**: 790-797
21 **Cornée J**, Pobel D, Riboli E, Guyader M, Hémon B. A case-control study of gastric cancer and nutritional factors in Marseille, France. *Eur J Epidemiol* 1995; **11**: 55-65
22 **Harrison LE**, Zhang ZF, Karpeh MS, Sun M, Kurtz RC. The role of dietary factors in the intestinal and diffuse histologic subtypes of gastric adenocarcinoma: a case-control study in the U.S. *Cancer* 1997; **80**: 1021-1028
23 **Houghton J**, Fox JG, Wang TC. Gastric cancer: laboratory bench to clinic. *J Gastroenterol Hepatol* 2002; **17**: 495-502
24 **Blanchard TG**, Czinn SJ. Review article: Immunological determinants that may affect the Helicobacter pylori cancer risk. *Aliment Pharmacol Ther* 1998; **12** Suppl 1: 83-90
25 **Blaser MJ**, Perez-Perez GI, Kleanthous H, Cover TL, Peek RM, Chyou PH, Stemmermann GN, Nomura A. Infection with Helicobacter pylori strains possessing cagA is associated with an increased risk of developing adenocarcinoma of the stomach. *Cancer Res* 1995; **55**: 2111-2115
26 **Kuipers EJ**, Pérez-Pérez GI, Meuwissen SG, Blaser MJ. Helicobacter pylori and atrophic gastritis: importance of the cagA status. *J Natl Cancer Inst* 1995; **87**: 1777-1780
27 **Nomura AM**, Lee J, Stemmermann GN, Nomura RY, Perez-Perez GI, Blaser MJ. Helicobacter pylori CagA seropositivity and gastric carcinoma risk in a Japanese American population. *J Infect Dis* 2002; **186**: 1138-1144
28 **Parsonnet J**, Friedman GD, Orentreich N, Vogelman H. Risk for gastric cancer in people with CagA positive or CagA negative Helicobacter pylori infection. *Gut* 1997; **40**: 297-301
29 **Rugge M**, Busatto G, Cassaro M, Shiao YH, Russo V, Leandro G, Avellini C, Fabiano A, Sidoni A, Covacci A. Patients younger than 40 years with gastric carcinoma: Helicobacter pylori genotype and associated gastritis phenotype. *Cancer* 1999; **85**: 2506-2511
30 **El-Omar EM**, Carrington M, Chow WH, McColl KE, Bream JH, Young HA, Herrera J, Lissowska J, Yuan CC, Rothman N, Lanyon G, Martin M, Fraumeni JF Jr, Rabkin CS. Interleukin-1 polymorphisms associated with increased risk of gastric cancer. *Nature* 2000; **404**: 398-402
31 **El-Omar EM**, Rabkin CS, Gammon MD, Vaughan TL, Risch HA, Schoenberg JB, Stanford JL, Mayne ST, Goedert J, Blot WJ, Fraumeni JF Jr, Chow WH. Increased risk of noncardia gastric cancer associated with proinflammatory cytokine gene polymorphisms. *Gastroenterology* 2003; **124**: 1193-1201
32 **Bidwell J**, Keen L, Gallagher G, Kimberly R, Huizinga T, McDermott MF, Oksenberg J, McNicholl J, Pociot F, Hardt C, D'Alfonso S. Cytokine gene polymorphism in human disease: on-line databases. *Genes Immun* 1999; **1**: 3-19
33 **Hamajima N**, Matsuo K, Saito T, Tajima K, Okuma K, Yamao K, Tominaga S. Interleukin 1 polymorphisms, lifestyle factors, and Helicobacter pylori infection. *Jpn J Cancer Res* 2001; **92**: 383-389
34 **Machado JC**, Pharoah P, Sousa S, Carvalho R, Oliveira C, Figueiredo C, Amorim A, Seruca R, Caldas C, Carneiro F, Sobrinho-Simões M. Interleukin 1B and interleukin 1RN polymorphisms are associated with increased risk of gastric carcinoma. *Gastroenterology* 2001; **121**: 823-829
35 **Figueiredo C**, Machado JC, Pharoah P, Seruca R, Sousa S, Carvalho R, Capelinha AF, Quint W, Caldas C, van Doorn LJ, Carneiro F, Sobrinho-Simões M. Helicobacter pylori and interleukin 1 genotyping: an opportunity to identify high-risk individuals for gastric carcinoma. *J Natl Cancer Inst* 2002; **94**: 1680-1687
36 **Machado JC**, Figueiredo C, Canedo P, Pharoah P, Carvalho R, Nabais S, Castro Alves C, Campos ML, Van Doorn LJ, Caldas C, Seruca R, Carneiro F, Sobrinho-Simões M. A proinflammatory genetic profile increases the risk for chronic atrophic gastritis and gastric carcinoma. *Gastroenterology* 2003; **125**: 364-371
37 **Furuta T**, El-Omar EM, Xiao F, Shirai N, Takashima M, Sugimura H. Interleukin 1beta polymorphisms increase risk of hypochlorhydria and atrophic gastritis and reduce risk of duodenal ulcer recurrence in Japan. *Gastroenterology* 2002; **123**: 92-105
38 **Tarlow JK**, Blakemore AI, Lennard A, Solari R, Hughes HN, Steinkasserer A, Duff GW. Polymorphism in human IL-1 receptor antagonist gene intron 2 is caused by variable numbers of an 86-bp tandem repeat. *Hum Genet* 1993; **91**: 403-404
39 **Rad R**, Prinz C, Neu B, Neuhofer M, Zeitner M, Voland P, Becker I, Schepp W, Gerhard M. Synergistic effect of Helicobacter pylori virulence factors and interleukin-1 polymorphisms for the development of severe histological changes in the gastric mucosa. *J Infect Dis* 2003; **188**: 272-281
40 **Palli D**, Saieva C, Luzzi I, Masala G, Topa S, Sera F, Gemma S, Zanna I, D'Errico M, Zini E, Guidotti S, Valeri A, Fabbrucci P, Moretti R, Testai E, del Giudice G, Ottini L, Matullo G, Dogliotti E, Gomez-Miguel MJ. Interleukin-1 gene polymorphisms and gastric cancer risk in a high-risk Italian population. *Am J Gastroenterol* 2005; **100**: 1941-1948
41 **Zeng ZR**, Hu PJ, Hu S, Pang RP, Chen MH, Ng M, Sung JJ. Association of interleukin 1B gene polymorphism and gastric cancers in high and low prevalence regions in China. *Gut* 2003; **52**: 1684-1689
42 **Garza-González E**, Bosques-Padilla FJ, El-Omar E, Hold G, Tijerina-Menchaca R, Maldonado-Garza HJ, Pérez-Pérez GI. Role of the polymorphic IL-1B, IL-1RN and TNF-A genes in distal gastric cancer in Mexico. *Int J Cancer* 2005; **114**: 237-241
43 **Tu S**, Bhagat G, Cui G, Takaishi S, Kurt-Jones EA, Rickman B, Betz KS, Penz-Oesterreicher M, Bjorkdahl O, Fox JG, Wang TC. Overexpression of interleukin-1beta induces gastric inflammation and cancer and mobilizes myeloid-derived suppressor cells in mice. *Cancer Cell* 2008; **14**: 408-419
44 **Kamangar F**, Abnet CC, Hutchinson AA, Newschaffer CJ, Helzlsouer K, Shugart YY, Pietinen P, Dawsey SM, Albanes D, Virtamo J, Taylor PR. Polymorphisms in inflammation-related genes and risk of gastric cancer (Finland). *Cancer Causes Control* 2006; **17**: 117-125
45 **Lee JY**, Kim HY, Kim KH, Kim SM, Jang MK, Park JY, Lee JH, Kim JH, Yoo JY. Association of polymorphism of IL-10 and TNF-A genes with gastric cancer in Korea. *Cancer Lett* 2005; **225**: 207-214
46 **Savage SA**, Abnet CC, Mark SD, Qiao YL, Dong ZW, Dawsey SM, Taylor PR, Chanock SJ. Variants of the IL8 and IL8RB genes and risk for gastric cardia adenocarcinoma and esophageal squamous cell carcinoma. *Cancer Epidemiol Biomarkers Prev* 2004; **13**: 2251-2257
47 **Canedo P**, Castanheira-Vale AJ, Lunet N, Pereira F, Figueiredo C, Gioia-Patricola L, Canzian F, Moreira H, Suriano G, Barros H, Carneiro F, Seruca R, Machado JC. The interleukin-8-251*T/*A polymorphism is not associated with risk for gastric carcinoma development in a Portuguese population. *Eur J Cancer Prev* 2008; **17**: 28-32
48 **Quintero E**, Pizarro MA, Rodrigo L, Piqué JM, Lanas A, Ponce J, Miño G, Gisbert J, Jurado A, Herrero MJ, Jiménez A, Torrado J, Ponte A, Díaz-de-Rojas F, Salido E. Association of Helicobacter pylori-related distal gastric cancer with the HLA class II gene DQB10602 and cagA strains in a southern European population. *Helicobacter* 2005; **10**: 12-21
49 **Navaglia F**, Basso D, Zambon CF, Ponzano E, Caenazzo L, Gallo N, Falda A, Belluco C, Fogar P, Greco E, Di Mario F, Rugge M, Plebani M. Interleukin 12 gene polymorphisms enhance gastric cancer risk in H pylori infected individuals. *J Med Genet* 2005; **42**: 503-510
50 **Hou L**, El-Omar EM, Chen J, Grillo P, Rabkin CS, Baccarelli A, Yeager M, Chanock SJ, Zatonski W, Sobin LH, Lissowska J, Fraumeni JF Jr, Chow WH. Polymorphisms in Th1-type cell-mediated response genes and risk of gastric cancer. *Carcinogenesis* 2007; **28**: 118-123
51 **Wu MS**, Wu CY, Chen CJ, Lin MT, Shun CT, Lin JT. Interleukin-10 genotypes associate with the risk of gastric carcinoma in Taiwanese Chinese. *Int J Cancer* 2003; **104**: 617-623
52 **Pociot F**, Mølvig J, Wogensen L, Worsaae H, Nerup J. A TaqI

polymorphism in the human interleukin-1 beta (IL-1 beta) gene correlates with IL-1 beta secretion in vitro. *Eur J Clin Invest* 1992; **22**: 396-402
53 **Hwang IR**, Kodama T, Kikuchi S, Sakai K, Peterson LE, Graham DY, Yamaoka Y. Effect of interleukin 1 polymorphisms on gastric mucosal interleukin 1beta production in Helicobacter pylori infection. *Gastroenterology* 2002; **123**: 1793-1803
54 **Santtila S**, Savinainen K, Hurme M. Presence of the IL-1RA allele 2 (IL1RN*2) is associated with enhanced IL-1beta production in vitro. *Scand J Immunol* 1998; **47**: 195-198
55 **Danis VA**, Millington M, Hyland VJ, Grennan D. Cytokine production by normal human monocytes: inter-subject variation and relationship to an IL-1 receptor antagonist (IL-1Ra) gene polymorphism. *Clin Exp Immunol* 1995; **99**: 303-310
56 **Wilkinson RJ**, Patel P, Llewelyn M, Hirsch CS, Pasvol G, Snounou G, Davidson RN, Toossi Z. Influence of polymorphism in the genes for the interleukin (IL)-1 receptor antagonist and IL-1beta on tuberculosis. *J Exp Med* 1999; **189**: 1863-1874
57 **Stokkers PC**, van Aken BE, Basoski N, Reitsma PH, Tytgat GN, van Deventer SJ. Five genetic markers in the interleukin 1 family in relation to inflammatory bowel disease. *Gut* 1998; **43**: 33-39
58 **Yamaoka Y**, Kita M, Kodama T, Sawai N, Tanahashi T, Kashima K, Imanishi J. Chemokines in the gastric mucosa in Helicobacter pylori infection. *Gut* 1998; **42**: 609-617
59 **Chang YW**, Jang JY, Kim NH, Lee JW, Lee HJ, Jung WW, Dong SH, Kim HJ, Kim BH, Lee JI, Chang R. Interleukin-1B (IL-1B) polymorphisms and gastric mucosal levels of IL-1beta cytokine in Korean patients with gastric cancer. *Int J Cancer* 2005; **114**: 465-471
60 **Takagi A**, Deguchi R, Kobayashi K, Miwa T. Cytokine expressions and H. pylori-associated gastric mucosal lesion. *Keio J Med* 2002; **51** Suppl 2: 51-52
61 **Hu S**, Song QB, Yao PF, Hu QL, Hu PJ, Zeng ZR, Pang RP. No relationship between IL-1B gene polymorphism and gastric acid secretion in younger healthy volunteers. *World J Gastroenterol* 2005; **11**: 6549-6553
62 **Lahner E**, Corleto VD, D'Ambra G, Di Giulio E, Delle Fave G, Annibale B. Is interleukin-1 genotyping useful for the clinical management of patients with atrophic body gastritis? *Aliment Pharmacol Ther* 2008; **27**: 355-365
63 **Sierra R**, Une C, Ramirez V, Alpizar-Alpizar W, Gonzalez MI, Ramirez JA, De Mascarel A, Cuenca P, Perez-Perez G, Megraud F. Relation of atrophic gastritis with Helicobacter pylori-CagA(+) and interleukin-1 gene polymorphisms. *World J Gastroenterol* 2008; **14**: 6481-6487
64 **Wang P**, Xia HH, Zhang JY, Dai LP, Xu XQ, Wang KJ. Association of interleukin-1 gene polymorphisms with gastric cancer: a meta-analysis. *Int J Cancer* 2007; **120**: 552-562
65 **Camargo MC**, Mera R, Correa P, Peek RM Jr, Fontham ET, Goodman KJ, Piazuelo MB, Sicinschi L, Zabaleta J, Schneider BG. Interleukin-1beta and interleukin-1 receptor antagonist gene polymorphisms and gastric cancer: a meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2006; **15**: 1674-1687
66 **Kamangar F**, Cheng C, Abnet CC, Rabkin CS. Interleukin-1B polymorphisms and gastric cancer risk--a meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2006; **15**: 1920-1928
67 **Loh M**, Koh KX, Yeo BH, Song CM, Chia KS, Zhu F, Yeoh KG, Hill J, Iacopetta B, Soong R. Meta-analysis of genetic polymorphisms and gastric cancer risk: variability in associations according to race. *Eur J Cancer* 2009; **45**: 2562-2568
68 **Glas J**, Török HP, Schneider A, Brünnler G, Kopp R, Albert ED, Stolte M, Folwaczny C. Allele 2 of the interleukin-1 receptor antagonist gene is associated with early gastric cancer. *J Clin Oncol* 2004; **22**: 4746-4752
69 **Al-Moundhri MS**, Al-Nabhani M, Al-Bahrani B, Burney IA, Al-Madhani A, Ganguly SS, Al-Yahyaee SA, Grant CS. Interleukin-1beta gene (IL-1B) and interleukin 1 receptor antagonist gene (IL-1RN) polymorphisms and gastric cancer risk in an Omani Arab population. *Gastric Cancer* 2006; **9**: 284-290
70 **Morgan DR**, Dominguez RL, Keku TO, Heidt PE, Martin CF, Galanko JA, Omofoye OA, Sandler RS. Gastric cancer and the high combination prevalence of host cytokine genotypes and Helicobacter pylori in Honduras. *Clin Gastroenterol Hepatol* 2006; **4**: 1103-1111
71 **He X**, Jiang L, Fu B, Zhang X. [Relationship between interleukin-1B and interleukin-1 receptor antagonist gene polymorphisms and susceptibility to gastric cancer] *Zhonghua Yi Xue Za Zhi* 2002; **82**: 685-688
72 **Chen A**, Li CN, Hsu PI, Lai KH, Tseng HH, Hsu PN, Lo GH, Lo CC, Lin CK, Hwang IR, Yamaoka Y, Chen HC. Risks of interleukin-1 genetic polymorphisms and Helicobacter pylori infection in the development of gastric cancer. *Aliment Pharmacol Ther* 2004; **20**: 203-211
73 **Schneider BG**, Camargo MC, Ryckman KK, Sicinschi LA, Piazuelo MB, Zabaleta J, Correa P, Williams SM. Cytokine polymorphisms and gastric cancer risk: an evolving view. *Cancer Biol Ther* 2008; **7**: 157-162
74 **Neale BM**, Sham PC. The future of association studies: gene-based analysis and replication. *Am J Hum Genet* 2004; **75**: 353-362
75 **Dong LM**, Potter JD, White E, Ulrich CM, Cardon LR, Peters U. Genetic susceptibility to cancer: the role of polymorphisms in candidate genes. *JAMA* 2008; **299**: 2423-2436
76 **Little J**, Sharp L, Masson LF, Brockton NT, Cotton SC, Haites NE, Cassidy J. Colorectal cancer and genetic polymorphisms of CYP1A1, GSTM1 and GSTT1: a case-control study in the Grampian region of Scotland. *Int J Cancer* 2006; **119**: 2155-2164
77 **Perri F**, Cotugno R, Piepoli A, Merla A, Quitadamo M, Gentile A, Pilotto A, Annese V, Andriulli A. Aberrant DNA methylation in non-neoplastic gastric mucosa of H. Pylori infected patients and effect of eradication. *Am J Gastroenterol* 2007; **102**: 1361-1371

S- Editor Li LF **L- Editor** Hughes D **E- Editor** Yang C