Influence of interleukin polymorphisms on development of gastric cancer and peptic ulcer

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Abstract

Pro-inflammatory cytokines are produced in the gastric mucosa by inflammatory cells activated by chronic Helicobacter pylori (H. pylori) infection. Polymorphisms of these cytokine genes are associated with individual differences in gastric mucosal cytokine mRNA level, which result in differences in gastric mucosal inflammation, acid inhibition and gastroduodenal disease risk in response to H. pylori infection. Although polymorphisms of interleukin (IL)-1B, IL-1RN and TNF-A have been reported to relate well with gastric cancer and peptic ulcer risk, those of IL-2, IL-4, IL-6 and IL-8 genes are unclear. In combined analyses using data from previous studies, we found that the risk of gastric non-cardia cancer development was significantly associated with IL-4-168 C allele (OR: 0.81, 95% CI: 0.69-1.00) and IL-4-450 T allele carrier status (0.61, 0.53-0.73), and IL-6-174 G/G genotype (2.02, 1.31-3.10). In peptic ulcer development, IL-2-330 G and IL-4-590 T allele carriers had a significantly decreased risk (0.37, 0.27-0.50 and 0.58, 0.34-0.99, respectively). Moreover, IL-2, IL-4, IL-6 and IL-8 gene genotypes prevalence differs among populations. The inflammatory cytokine gene polymorphisms (e.g. IL-4-590 and IL-6-572 for gastric cancer, and IL-4-590, IL-6-572 and IL-8-251 for peptic ulcer) have a more potent influence on development of gastroduodenal diseases in Western than East Asian populations. These cytokine gene polymorphisms, as well as those of IL-1B, IL-1RN and TNF-A, may be used to identify groups at higher risk of gastric cancer and peptic ulcer, and those suitable for their prevention by H. pylori eradication therapy in Western populations.

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Key words: Helicobacter pylori; Cytokines; Genetic polymorphism; Stomach neoplasms; Peptic ulcer

INTRODUCTION

Helicobacter pylori (H. pylori) infects > 50% of the world’s population, and is particularly prevalent in developing countries (> 90%). Chronic H. pylori infection relates not only to the development of upper gastrointestinal diseases, such as peptic ulcer diseases, gastric adenoma, gastric cancer, and gastric mucosa-associated lymphoid tissue lymphoma, but also with some extra-gastrointestinal disorders, such as idiopathic thrombocytopenic purpura, chronic idiopathic urticaria and iron-deficiency anemia. Prevention and treatment of H. pylori-related disease has therefore relied on eradication therapy as first-line treatment.
The key pathophysiological event in *H. pylori* infection of gastric mucosa is the induction of a gastric mucosal inflammatory response. Following infection, neutrophils and mononuclear cells activated by *H. pylori* and their products infiltrate *H. pylori*-infected gastric mucosa and stimulate the transcription and synthesis of several pro-inflammatory cytokines e.g. interleukin (IL)-1β, IL-2, IL-6, IL-8 and tumor necrosis factor (TNF)-α and anti-inflammatory cytokines e.g. IL-4 and IL-10[13]. The increased production of inflammatory cytokines in response to *H. pylori* infection results in enhanced gastric mucosal inflammation, through binding to specific receptors on target cells.

Most of these inflammatory cytokine genes have genetic variations that influence cytokine levels in the gastric mucosa. Levels of mucosal IL-1β, for example, the most studied inflammatory cytokine, differ significantly among the different genotypes in three polymorphisms, IL-1B-511, -31 and IL-1RN[14]. Carriers of the IL-1B-511 T, -31 C and IL-1RN *2* alleles have significantly higher IL-1β levels than those of the other allele[13]. Consistent with this difference, carriers of the IL-1B-511 T, IL-1B-31 C alleles and IL-1RN *2/*2 (2 repeats of 86 bp) genotype show enhanced suppression of gastric acid secretion, which results in more rapid development of gastric atrophy, and a consequently greater risk of developing gastric cancer than in those with the IL-1B-511 C, IL-1B-31 T and IL-1RN*1* alleles[13-18]. However, although IL-2, IL-4, IL-6 and IL-8 levels in gastric mucosa are reported to increase in patients with *H. pylori* infection[19,20], it remains unknown whether these inflammatory cytokine polymorphisms are associated with gastroduodenal disease development in a similar way as those with IL-1B and TNF-α. Previously reported associations with disease risk and cytokine gene polymorphisms of IL-2, IL-4, IL-6 and IL-8 are controversial, however, owing to either or both type 2 error and geographical differences (Tables 1-4).

Here, we review differences in the risk of development of peptic ulcer and gastric cancer by different inflammatory cytokine gene polymorphisms of IL-2, IL-4, IL-6 and IL-8.

**ILI-2 POLYMORPHISM AND GASTRODUODENAL DISEASES**

IL-2, a 15-kDa α-helical cytokine of the Th1 type produced exclusively by activated T cells, promotes the proliferation of lymphocytes, macrophages and NK cells[21]. IL-2 potently regulates the immune response, and plays important roles in the differentiation of CD41-positive T cells into Th1 and Th2 effector subsets, while inhibiting T-helper 17 differentiation[22,23]. In T cells, IL-2 binding to the IL-2 receptor activates the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway, as well as mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) signaling, which results in the transcription of pro-inflammatory cytokine genes. Through these pathways, IL-2 upregulates the expression of CD25 and IL-2Rβ, modulates genes involved in cell cycle regulation, and promotes T-cell survival and differentiation into effector and memory cells[24,25]. IL-2 contributes to the induction and transmission of inflammatory immune responses, including *H. pylori*-induced gastric inflammation.

Two kinds of single nucleotide polymorphism (SNP) occur in IL-2-330 and -384 (4q26-q27) of the promoter region, which affect IL-2 production[22,27]. IL-2 expression level with deletion of the IL-2-289 to -361 region was significantly decreased compared with that with the normal gene. IL-2-330 polymorphism located in this region is therefore considered to have particular influence on IL-2 levels[26,27]. In fact, IL-2 production in the IL-2-330 G/G genotype is about threefold greater than that of the IL-2-330 T/G or T/T genotypes in healthy subjects[28]. Consistent with this difference, an association between the IL-2-330 polymorphism and susceptibility to some inflammatory and immune diseases, such as rheumatoid arthritis, psoriasis and multiple sclerosis, has been reported[29-31]. IL-2 is therefore also thought to induce *H. pylori*-associated gastroduodenal diseases by regulating Th1 immune responses[32] and inhibiting gastric acid secretion[13].

Four studies have investigated the associations with IL-2-330 (three studies), +114 (one study) and +384 (one study) polymorphisms and development of atrophic gastritis (one study), peptic ulcer (one study) or gastric cancer (three studies) (Table 1)[34-37]. With regard to IL-2-330 polymorphism, Wu et al[37] have reported that subjects carrying the T allele, a low producer allele, have a significantly reduced risk of gastric cardia cancer (OR: 0.68, 95% CI: 0.46-0.99) compared with those with the G/G genotype. IL-2-330 polymorphisms may contribute to the etiology of gastric cardia cancer in Chinese populations[37]. However, Shin et al[31] failed to demonstrate a significant association with IL-2-330 polymorphism and gastric cancer development in the Chinese, while Togawa et al[34] conversely have reported that the IL-2-330 T/T genotype increased the risk of gastric cancer-related gastric atrophy (OR: 2.78, 95% CI: 1.26-6.17) in the Japanese. The results for IL-2-330 polymorphism are thus controversial. Moreover, no significant association was seen for IL-2-384 and +114 polymorphisms and gastric cancer development[36].

When combined, the results of previous studies of IL-2-330 polymorphism[34,35,37] surprisingly have shown that the risk of peptic ulcer development is 0.57 (95% CI: 0.33-0.98) for the G/G genotype and 0.37 (0.27-0.50) for G allele carriers compared with the T/T genotype (Table 5). However, no association with IL-2-330 polymorphism was seen for the risk of gastric non-cardia cancer. This finding is inconsistent with the first hypothesis, which states that patients with the IL-2 high producer genotype have an increased risk of gastric cancer and gastric ulcer development. Togawa et al[34] have speculated that one possible reason is that a higher IL-2 level is thought to enhance the immune response to eradicate *H. pylori*, and thereby decrease gastric mucosal inflammation. Moreover, an IL-2 promoter construct in a cell line shows higher levels of gene expression with
the IL-2-330 G allele, whereas the transcriptional effect of this polymorphism in lymphocytes shows that the IL-2-330 G allele is associated with a lower expression of IL-2\(^{[30]}\). In fact, many studies have shown that the IL-2-330 T/T genotype increases the risk of a number of diseases, such as Takayasu’s disease\(^{[38]}\), subacute sclerosing panencephalitis\(^{[39]}\) and schizophrenia\(^{[40]}\).

All studies that have investigated the relationship of IL-2-330 polymorphism and disease development to date were in Asian populations\(^{[34,35,37]}\). Further studies, including those in Western populations, will be necessary to solve this discrepancy and establish this relationship.

### IL-4 POLYMORPHISM AND GASTRODUODENAL DISEASES

IL-4 is an anti-inflammatory cytokine, which inhibits gastric mucosal *H. pylori*-induced inflammation and atrophy by decreasing interferon γ (IFN-γ), which plays an important role in Th1 immune responses. IL-4 also plays a central role in the maturation of T-helper cells to the Th2 phenotype. With a shift from a Th1 to a Th2 cell pattern, IL-4 can enhance the production of anti-inflammatory cytokines (e.g. IL-10 and IL-13), including that of IL-4\(^{[41,42]}\), and suppress the production of monocyte-derived pro-

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**Table 1  Association of IL-2 polymorphism and gastroduodenal diseases**

| Position | Disease | Authors | Year | n | T/T | T/G | G/G |
|----------|---------|---------|------|---|-----|-----|-----|
| -330 T/G | GC      | Wu et al\(^{[37]}\) | 2009 | 1026 | 491 | 441 | 94  |
|          | NUD     | 1083   | 516  | 480 | 87  |
|          | GC      | Shin et al\(^{[41]}\) | 2008 | 122  | 79  | 35  | 8   |
|          | NUD     | 100    | 72   | 16  | 12  |
|          | PU      | Shin et al\(^{[41]}\) | 2008 | 220  | 159 | 45  | 16  |
|          | NUD     | 100    | 72   | 16  | 12  |
|          | Atrophy | Togawa et al\(^{[46]}\) | 2005 | 352  | 80  | 63  | 9   |
|          | NUD     | 443    | 202  | 196 | 45  |
| -384 G/T | GCC     | Savage et al\(^{[44]}\) | 2004 | 87   | 16  | 47  | 20  |
|          | NUD     | 379    | 96   | 174 | 109 |
| +114 G/T | GCC     | Savage et al\(^{[44]}\) | 2004 | 82   | 33  | 35  | 14  |
|          | NUD     | 377    | 149  | 148 | 80  |

GC: Gastric cancer; GCC: Gastric cardia cancer; PU: Peptic ulcer; IL: Interleukin; NUD: Non-ulcer dyspepsia; NS: Not significant.

**Table 2  Association of IL-4 polymorphism and gastroduodenal diseases**

| Position | Disease | Authors | Year | n | T/T | T/C | C/C |
|----------|---------|---------|------|---|-----|-----|-----|
| -168 T/C | GC      | Wu et al\(^{[37]}\) | 2009 | 1042 | 744 | 271 | 27  |
|          | NUD     | 1099   | 743  | 332 | 24  |
| -590 C/T | GC      | Zambon et al\(^{[47]}\) | 2008 | 40   | 32  | 7   | 1   |
|          | NUD     | 171    | 124  | 43  | 4   |
| GC       | García-González et al\(^{[34]}\) | 2007 | 404  | 283 | 107 | 14  |
|          | NUD     | 404    | 267  | 123 | 14  |
| GC       | Lai et al\(^{[44]}\) | 2005 | 123  | 83  | 38  | 2   |
|          | NUD     | 162    | 105  | 50  | 7   |
| GC       | El-Omar et al\(^{[41]}\) | 2003 | 122  | 78  | 37  | 7   |
|          | NUD     | 209    | 153  | 46  | 10  |
| GC       | Wu et al\(^{[46]}\) | 2003 | 220  | 146 | 69  | 5   |
|          | NUD     | 230    | 163  | 55  | 12  |
| GC       | Zambon et al\(^{[47]}\) | 2008 | 171  | 124 | 43  | 4   |
|          | NUD     | 107    | 79   | 26  | 2   |
| Atrophy  | Kato et al\(^{[46]}\) | 2006 | 788  | 398 | 308 | 82  |
|          | Dys     | 115    | 51   | 48  | 16  |
|          | NUD     | 1020   | 506  | 414 | 100 |
| -33 C/T  | Atrophy | Togawa et al\(^{[46]}\) | 2005 | 157  | 10  | 70  | 77  |
|          | NUD     | 452    | 183  | 227 | 7   |
|          | 984, 2983 |       | 100  | 52  | 29  | 7   |
|          | 93      | 40     | 27   | 17  |

Although Seno et al\(^{[55]}\) investigated nine SNPs (IL-4-590, -33, 3437, 3557, 4047, 4144, 4271, 4367 and 8427), data concerning the exclusion of IL-4+984 and 2983 were unclear. Dys: Dysplasia; DU: Duodenal ulcer.
inflammatory cytokines (e.g. IL-1β, IL-6 and IL-8)\(^{42}\).

IL-4 is overproduced in *H. pylori*-infected gastric mucosa. However, gastric mucosal inflammation has been shown to significantly reduce IL-4 administration\(^{43,44}\), and IL-4-deficient mice infected with *H. pylori* show severe gastric inflammation compared with wild-type mice\(^{45-47}\). A balance between Th1 and Th2 cytokines by IL-4 therefore crucially influences the outcome of *H. pylori* infection. Moreover, IL-4 is reportedly associated with cancer development via its suppression of inflammation, and directly inhibits the growth of human melanoma, renal cell carcinoma and gastric cancer cells\(^{48}\).

The family of the IL-4 gene, which encodes IL-4, is located on chromosome 5q31-33, which contains the IL-3, IL-4, IL-5, IL-9, IL-13, IL-15 genes as well as the interferon-regulatory factor and granulocyte-macrophage colony-stimulating factor (GM-CSF)\(^{49}\). There are two common polymorphisms in the IL-4 gene, -590 C/T and a 70-bp sequence variant tandem repeat at intron 3; and many minor polymorphisms, such as -168, -33, 3437, 3557, 4047, 4144, 4271, 4367, 8427\(^{50,51}\). The IL-4-590 polymorphism is located upstream of all known control elements of IL-4, such as the negative regulatory element, the NF-κB recognition sequence, and the TATA box\(^{49}\). Individuals with the IL-4-590 T/T genotype can produce IL-4 at higher levels than those with the C/C genotype\(^{48}\). IL-4 polymorphism is reportedly associated with the risk of cancer development (e.g. colorectal cancer\(^{49}\)), and the Th2 T-cell response represented by IL-4 is expected to play a protective role in the development of cancer.

Seven studies have investigated the association of IL-4-590 polymorphism and atrophic gastritis (one study\(^{52}\)), gastric cancer (five studies\(^{53-56}\)), and duodenal ulcer development (one study\(^{57}\) (Table 2). In 2003, Wu et al\(^{58}\) first reported that a higher prevalence of diffuse-type gastric cancer (OR: 1.64, 95% CI: 1.01-2.67), particularly in gastric cardia cancer (2.44, 1.13-5.27), is observed in IL-4-590 C allele carriers, a low producer allele, compared with the IL-4-590 T/T genotype, which suggests that low production of IL-4 is responsible for the development of gastric cancer. However, other studies have failed to demonstrate any significant association of IL-4 polymorphisms with disease risk\(^{59-61}\). In a combined-analysis of IL-4-590 C/T polymorphism\(^{52-56}\), however, the risk of gastric non-cardia cancer development was 0.68 (95% CI: 0.57-0.80) for the C/T genotype, 0.36 (0.24-0.53) for the T/T genotype and 0.61 (0.53-0.73) for T allele carriers (Table 6). Moreover, the risk of peptic ulcer development in T allele carriers (0.58, 0.34-0.99) was significantly lower (Table 6). This protective effect of IL-4-590 polymorphism is therefore

\(\text{Table 3 Association of IL-4 polymorphism and gastroduodenal diseases}\)

| Position | Disease | Authors | Year | n | C/C | C/G | G/G |
|----------|---------|---------|------|---|-----|-----|-----|
| -174 C/G | GC      | Gatti et al\(^{49}\) | 2007 | GC | 56  | 1   | 13  | 42  |
|          | NUD     | 112    | 11  | 53 | 48  |
| GCC      | Deans et al\(^{50}\) | 2007 | GC | 197 | 43  | 83  | 71  | NS  |
|          | NUD     | 224    | 44  | 101| 79  |
| GC       | Kamangar et al\(^{51}\) | 2006 | GC | 102 | 27  | 54  | 21  | GC: 2.2 (1.2-4.0) vs G/G |
|          | NUD     | 152    | 43  | 58 | 51  |
| GC       | El-Omar et al\(^{52}\) | 2003 | GC | 123 | 16  | 52  | 55  | NS  |
|          | NUD     | 209    | 28  | 98 | 83  |
| GC       | Hwang et al\(^{53}\) | 2003 | GC | 60  | 2   | 9   | 49  | -   |
| PU       | Chakravorty et al\(^{54}\) | 2008 | GU | 91  | 1   | 18  | 72  | NS  |
|          | NUD     | 62     | 1   | 7  | 54  |
| DU       | Hwang et al\(^{55}\) | 2003 | DU | 60  | 0   | 0   | 30  | -   |
|          |         |        |     |    | C/C | C/G | G/G |
| GC       | Kang et al\(^{56}\) | 2009 | GC | 284 | 154 | 113 | 17  | NS  |
|          | NUD     | 278    | 140 | 123| 15  |
| GC       | Hwang et al\(^{57}\) | 2003 | GC | 60  | 19  | 29  | 12  | -   |
| PU       | Kang et al\(^{58}\) | 2009 | PU | 434 | 249 | 167 | 20  | DU: GG 0.3 (0.1-0.9) |
|          | NUD     | 278    | 140 | 123| 15  |
| PU       | Chakravorty et al\(^{54}\) | 2008 | PU | 91  | 57  | 27  | 7   | NS  |
|          | NUD     | 62     | 37  | 20 | 5   |
| DU       | Hwang et al\(^{59}\) | 2003 | DU | 60  | 21  | 20  | 19  | -   |
| GC       | Kamangar et al\(^{60}\) | 2006 | GC | 110 | 25  | 59  | 26  | NS  |
|          | NUD     | 203    | 61  | 86 | 56  |
| GC       | Hwang et al\(^{61}\) | 2003 | GC | 60  | 50  | 8   | 2   | -   |
| PU       | Chakravorty et al\(^{62}\) | 2008 | PU | 91  | 53  | 29  | 10  | NS  |
|          | NUD     | 62     | 41  | 16 | 5   |
| DU       | Hwang et al\(^{63}\) | 2003 | GC | 60  | 52  | 8   | 0   | -   |
| GC       | Liao et al\(^{64}\) | 2008 | GC | 155 | 96  | 55  | 4   | NS  |
|          | NUD     | 211    | 118 | 84 | 9   |

Although Kang et al and Savage et al investigated the association with IL-6-174 C/G polymorphism and gastric cancer, data were not described in detail (>99% of patients were of the IL-6-174 C/G genotype).

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significant for gastric non-cardia cancer and peptic ulcer patients with a higher producer genotype.

The prevalence of IL-4-590 C/C, C/T and T/T genotypes differs between Western and Asian populations (Table 7). The prevalence of C/C, C/T and T/T genotypes in a Western population with gastric cancer was 69.8% (362/518), 26.1% (135/) and 4.1% (21/), respectively, whereas in those with non-ulcer dyspepsia (NUD) was 55.9% (1448/2592), 36.0% (934/) and 8.1% (210/). In a Western population, the risks for gastric non-cardia cancer and peptic ulcer development were 0.55 (95% CI: 0.46-0.67) and 0.35 (0.32-0.94) for T allele carriers, respectively (Table 8). In an Asian population, in contrast, no significant difference was seen between subjects with gastric cancer and NUD. This difference in the influence of IL-4-590 polymorphism on disease development

Table 4 Association of IL-4 polymorphism and gastroduodenal diseases

| Disease       | Authors                      | Year | n   | T/T   | T/A   | A/A   |
|---------------|------------------------------|------|-----|-------|-------|-------|
| -251 A/T      | Kang et al[89]               | 2009 | GC  | 284   | 106   | 136   | 43    | AA: 2.0 (1.2-3.6) |
|               | NUD                          |      | 275 | 125   | 125   | 25    |       |
|               | Canedo et al[89]             | 2008 | GC  | 333   | 111   | 169   | 53    | NS    |
|               | NUD                          |      | 880 | 265   | 445   | 170   |       |
|               | Garza-Gonzalez et al[90]     | 2007 | GC  | 78    | 15    | 47    | 16    | A carrier: 2.1 (1.1-4.2) |
|               | NUD                          |      | 230 | 76    | 107   | 47    |       |
|               | Kamali-Sarvestani et al[90]  | 2006 | GC  | 19    | 4     | 6     | 9     | AT: 4.5 (1.5-12.9) |
|               | NUD                          |      | 153 | 57    | 174   | 22    |       |
|               | Shirai et al[90]             | 2006 | GC  | 181   | 83    | 78    | 20    | MSL (+): TT 5.2 (1.5-18.0) |
|               | NUD                          |      | 268 | 211   | 208   | 49    |       |
|               | Savage et al[90]             | 2006 | GC  | 287   | 71    | 140   | 76    | NS    |
|               | NUD                          |      | 426 | 106   | 205   | 117   |       |
|               | Kamangar et al[90]           | 2006 | GC  | 112   | 42    | 56    | 14    | NS    |
|               | NUD                          |      | 207 | 72    | 111   | 24    |       |
|               | Taguchi et al[91]            | 2005 | GC  | 396   | 161   | 191   | 44    | AA: 2.2 (1.1-4.6) |
|               | NUD                          |      | 252 | 125   | 105   | 22    |       |
|               | Lee et al[91]                | 2005 | GC  | 470   | 198   | 213   | 59    | TT: 1.9 (1.3-3.0) |
|               | NUD                          |      | 308 | 108   | 138   | 62    |       |
|               | Ohyauchi et al[91]           | 2005 | GC  | 212   | 93    | 106   | 13    | A carrier: 1.8 (1.1-2.8) |
|               | NUD                          |      | 195 | 106   | 74    | 15    |       |
|               | Savage et al[92]             | 2004 | GC  | 88    | 26    | 39    | 23    | AA: 2.0 (1.0-3.8) |
|               | NUD                          |      | 429 | 147   | 207   | 75    |       |
|               | Lu et al[92]                 | 2005 | GC  | 250   | 94    | 102   | 54    | AA: 1.9 (1.2-3.2) |
|               | NUD                          |      | 300 | 119   | 144   | 37    |       |
|               | Kang et al[93]               | 2009 | PU  | 447   | 160   | 223   | 64    | GU: AA: 2.7 (1.5-4.8) |
|               | NUD                          |      | 275 | 125   | 125   | 25    |       |
|               | Garza-Gonzalez et al[91]     | 2007 | PU  | 29    | 11    | 14    | 4     | NS    |
|               | NUD                          |      | 230 | 76    | 107   | 47    |       |
|               | Kamali-Sarvestani et al[91]  | 2006 | GU  | 61    | 19    | 28    | 14    | NS    |
|               | NUD                          |      | 153 | 57    | 74    | 22    |       |
|               | Ohyaauchi et al[91]          | 2005 | PU  | 283   | 134   | 127   | 22    | GU:A carrier: 1.8 (1.1-3.0) |
|               | NUD                          |      | 195 | 106   | 74    | 15    |       |
|               | Chakravorty et al[94]         | 2008 | PU  | 91    | 20    | 46    | 25    | NS    |
|               | NUD                          |      | 62  | 18    | 28    | 16    |       |
|               | Hofner et al[101]            | 2007 | DU  | 85    | 15    | 49    | 21    | AA: 2.3 (1.5-6.4) |
|               | NUD                          |      | 211 | 61    | 106   | 44    |       |
|               | Gylai et al[102]             | 2004 | DU  | 69    | 11    | 45    | 13    | A carrier: 4.4 (1.9-10.5) |
|               | NUD                          |      | 47  | 21    | 17    | 9     |       |
|               | Leung et al[103]             | 2006 | IM  | 123   | 23    | 56    | 44    | NS    |
|               | NUD                          |      | 179 | 36    | 92    | 51    |       |
|               | Taguchi et al[104]           | 2005 | Atrophy | 215   | 90    | 99    | 26    | AA: 2.4 (1.1-4.9) |
|               | NUD                          |      | 252 | 125   | 105   | 22    |       |
|               | Hamajima et al[105]          | 2003 | GC  | 111   | 42    | 55    | 14    | NS    |
|               | NUD                          |      | 208 | 72    | 112   | 24    |       |
|               | Kamangar et al[90]           | 2006 | GC  | 86    | 29    | 33    | 24    | GG: 2.1 (1.1-3.9) |
|               | NUD                          |      | 402 | 152   | 181   | 69    |       |
|               | Savage et al[106]            | 2004 | GC  | 111   | 47    | 52    | 12    | NS    |
|               | NUD                          |      | 208 | 81    | 105   | 22    |       |
|               | Kamangar et al[90]           | 2006 | GC  | 85    | 28    | 41    | 16    | NS    |
|               | NUD                          |      | 406 | 167   | 177   | 62    |       |

Although Seno et al[95] investigated six SNPs (IL-4-352, 289, 294, 680, 2217 and 2670), data were not described in detail. IM: Intestinal metaplasia.

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may have a geographic basis, and the effect appears to be stronger in Western populations (Table 8).

With regard to minor polymorphisms of IL-4, IL-4-168, -33, 984/2983 SNPs have been reported by one study each \cite{34,37,55}. Compared with the IL-4-168 C/C high producer genotype \cite{37}, the IL-4-168 T allele carrier was associated with a significantly decreased gastric cancer risk (OR: 0.83, 95% CI: 0.69-1.00). Further, this significant protective effect was also seen for gastric cardia cancer patients (0.73, 0.56-0.95) \cite{37}.

Thus, a significant protective effect against gastric non-cardia cancer was seen with the higher producer genotype IL-4-590 and -168 polymorphisms, particularly in Western populations.

Table 5  ORs for gastric non-cardia cancer and peptic ulcer development in IL-2-330 polymorphism

| Genotype | T/T | T/G | G/G | OR | 95% CI | P value | T/T | T/G | G/G | OR | 95% CI | P value |
|----------|-----|-----|-----|----|--------|---------|-----|-----|-----|----|--------|---------|
| IL-2-330 | 755 | 209 | 77  | 0.77 | 0.52-1.14 | 0.20 | 16  | 0.57 | 0.33-0.98 | 0.04 | 159 | 0.74-1.11 | 0.33 |

\textsuperscript{1}NUD includes gastritis without gastric cancer and peptic ulcer, and atrophic gastritis patients. Because we deleted a number of gastric cardia cancer patients, a number of cancer patients shown in this Table do not match that in Table 1.

Table 6  ORs for gastric non-cardia cancer and peptic ulcer development with IL-4-168 and -590 polymorphisms

| Genotype | T/T | T/C | C/C | OR | 95% CI | P value | T/T | T/C | C/C | OR | 95% CI | P value |
|----------|-----|-----|-----|----|--------|---------|-----|-----|-----|----|--------|---------|
| IL-4-168 | 743 | 744 | 0.81 | 0.67-0.98 | 0.03 | 743 | 744 | 0.81 | 0.67-0.98 | 0.03 |
| IL-4-590 | 1716 | 591 | 0.68 | 0.57-0.80 | <0.01 | 46  | 46  | 0.68 | 0.57-0.80 | <0.01 |

\textsuperscript{1}NUD includes patients with gastritis without gastric cancer and peptic ulcer, and atrophic gastritis. Because we deleted a number of gastric cardia cancer patients, the number of cancer patients in this Table does not match that in Table 2.

Table 7  Prevalence of inflammatory cytokine gene genotypes in East Asian and Western populations

| Gene | Population | NUD T/T | T/G | G/G | GC T/T | T/G | G/G | PU T/T | T/G | G/G |
|------|------------|--------|-----|-----|--------|-----|-----|--------|-----|-----|
| IL-2-330 | Asian | 870 | 755 | 153 | 258 | 209 | 35 | 159 | 45 | 16 |
| IL-2-330 | Western | 870 | 755 | 153 | 258 | 209 | 35 | 159 | 45 | 16 |
| IL-4-590 | Asian | 268 | 105 | 19 | 229 | 107 | 7 | 229 | 107 | 7 |
| IL-4-590 | Western | 1448 | 934 | 210 | 362 | 135 | 21 | 362 | 135 | 21 |
| IL-6-174 | Asian | 126 | 310 | 261 | 34 | 82 | 112 | 1 | 26 | 94 |
| IL-6-174 | Western | 126 | 310 | 261 | 34 | 82 | 112 | 1 | 26 | 94 |
| IL-6-572 | Asian | 37 | 20 | 5 | 3 | 16 | 11 | 2 | 6 | 5 |
| IL-6-572 | Western | 37 | 20 | 5 | 3 | 16 | 11 | 2 | 6 | 5 |
| IL-6-597 | Asian | 102 | 102 | 61 | 45 | 67 | 28 | 75 | 37 | 10 |
| IL-6-597 | Western | 102 | 102 | 61 | 45 | 67 | 28 | 75 | 37 | 10 |
| IL-6-818 | Asian | 152 | 181 | 69 | 30 | 0 | 0 | 30 | 0 | 0 |
| IL-6-818 | Western | 152 | 181 | 69 | 30 | 0 | 0 | 30 | 0 | 0 |
| IL-6+396 | Asian | 1324 | 1425 | 443 | 735 | 826 | 233 | 394 | 86 | 394 | 86 |
| IL-6+396 | Western | 1324 | 1425 | 443 | 735 | 826 | 233 | 394 | 86 | 394 | 86 |
| IL-6+781 | Asian | 72 | 112 | 24 | 27 | 43 | 12 | 27 | 43 | 12 |
| IL-6+781 | Western | 72 | 112 | 24 | 27 | 43 | 12 | 27 | 43 | 12 |
| IL-8-251 | Asian | 167 | 177 | 62 | 29 | 41 | 11 | 29 | 41 | 11 |
| IL-8-251 | Western | 167 | 177 | 62 | 29 | 41 | 11 | 29 | 41 | 11 |

Thus, a significant protective effect against gastric non-cardia cancer was seen with the higher producer genotype IL-4-590 and -168 polymorphisms, particularly in Western populations.

IL-6 POLYMORPHISM AND GASTRODUODENAL DISEASES

IL-6, a multifunctional cytokine produced by immune and...
many non-immune cells including monocytes, lymphocytes, macrophages, and endothelial and intestinal epithelial cells, functions as both an inflammatory mediator and endocrine regulator\(^{59}\). IL-6 plays an important role in host defense mechanisms as a messenger between innate and adaptive systems, by stimulating IFN-γ production in T cells and promoting immunoglobulin secretion in activated B cells\(^{59}\).

High serum levels of IL-6 family cytokines have been reported in various gastrointestinal cancer cells\(^{60}\). IL-6 and IL-11 belong to the IL-6 cytokine family, which includes ciliary neurotrophic factor, cardiotrophin-1, cardiotrophin-like cytokine, leukemia inhibitory factor, oncostatin M, and IL-27. These act as ligands for the signaling receptor subunit gp130\(^{61}\). IL-6 requires specific α receptor subunits and gp130 homodimers of signal transducing receptor\(^{62}\). Recently, mice with a mutation in gp130 (gp130 757/757 mouse) have been established to enhance chronic gastric inflammation and develop gastric neoplasms without H. pylori infection, via an imbalance between STAT3 and Y-759/SHP-2 signaling\(^{63}\). The presence of the Y757F mutation in the gp130 receptor promotes the failure of SHP-2 phosphorylation and subsequent activation of the pro-apoptotic Ras/Erk and PI3K/AKT pathways, which results in massive STAT3 activation. STAT3 hyperactivity suppresses the cytostatic effect of the stroma on cell proliferation\(^{64}\). Moreover, STAT3 also induces epithelial cell expression of IL-11\(^{65}\). These signaling events promote an oncogenic program in which the expression of anti-apoptotic, pro-angiogenic, and pro-proliferative genes results in inflammation-associated gastric tumorigenesis\(^{66}\). The IL-6 family signaling system is therefore an attractive research target in gastric cancer pathogenesis.

Mucosal IL-6 levels increase in H. pylori-associated gastritis\(^{66,67}\) and dramatically decrease after eradication of infection\(^{68}\). IL-6 mRNA levels in gastric mucosa correlate with the level of gastric mucosal inflammation\(^{67,69}\). Serum levels of IL-6 are higher in patients with gastric cancer than gastritis\(^{70}\). IL-6 plays an important role as a prognostic factor in advanced gastric cancer and lymph node metastasis\(^{71}\), and a serum IL-6 level > 13 pg/mL correlates with tumor progression and poor survival after resection\(^{72}\).

The IL-6 gene is located on chromosome 7p21 and the SNPs at the 5’ flanking region of the IL-6 promoter have been identified as IL-6-174, -572 and -597\(^{73}\). IL-6-174 G allele carriers produce higher levels of IL-6 than those with the C/C genotype\(^{74}\), and have a higher prevalence of systemic juvenile-onset chronic arthritis, lipid abnormalities\(^{75}\) and insulin resistance\(^{76}\). IL-6-174 G and -597 G allele carriers are closely linked regardless of ethnic group or disease status\(^{77}\). The IL-6-572 G allele is also associated with a higher serum IL-6 level than IL-6-572 C/C allele\(^{78}\), and is a risk factor for diabetic nephropathy and lung cancer with asthma/atopy\(^{79,80}\).

Six studies of the IL-6-174 polymorphism\(^{53,77,81-84}\), three of IL-6-572\(^{77,84}\), three of IL-6-597\(^{77,83,84}\) and one of IL-6-634\(^{77}\) in relation to the development of gastric cancer and peptic ulcer have appeared (Table 3). Gatti et al\(^{81}\) have reported that the IL-6-174 G allele carriers account for a significantly higher incidence of gastric cancer than NUD patients (98.2%, 55/56 and 90.2%, 101/112, respectively). However, Kamangar et al\(^{80}\) have demonstrated that, compared with G/G genotype IL-6, the low producer genotype IL-6-174G/C has an increased risk of gastric cancer, while other studies have shown no significant relationship of IL-6-174 polymorphism with gastric diseases. The association of this polymorphism with these conditions thus remains unclear. In contrast, frequencies of the IL-6-572 G/G genotype (OR: 0.3, 95% CI: 0.1-0.9) and of G allele carriers (0.5, 0.4-0.8) are lower in H. pylori-positive patients with duodenal ulcer than in those with NUD\(^{80}\).

In a combined analysis of IL-6-174 C/G polymorphism\(^{13,53,81,84}\), the risk of gastric non-cardia cancer was 2.02 (1.31-3.10) for the G/G compared with C/C genotype (Table 9). Moreover, the risk of gastric ulcer...
IL-8 POLYMORPHISM AND GASTRODUODENAL DISEASES

IL-8, a member of the CXC chemokine family, which was originally identified as a potent chemoattractant for neutrophils and lymphocytes, induces not only cell proliferation and migration, but also angiogenesis. IL-8 is produced by gastric epithelial cells during H. pylori infection, particularly in the cag-pathogenicity-island-positive strain of H. pylori, one of the major virulence factors. In addition, IL-8 protein levels are 10-fold higher in gastric cancer than in normal gastric tissue, and directly correlate with the vascularity of the tumors. The transfection of gastric cancer cells with the IL-8 gene enhances their tumorigenesis and angiogenesis in the gastric wall of nude mice. Increased IL-8 levels may amplify the inflammatory response to H. pylori by recruiting neutrophils and monocytes, thereby resulting in an advanced degree of gastritis, which ultimately predisposes to the development of gastric cancer.

There are three common polymorphisms in the IL-8 gene, -251 A/T, 396 T/G and 781 C/T polymorphisms. Among these, IL-8-251 A allele carrier status is associated with increased IL-8 production. Consistent with these differences, IL-8-251 polymorphism influences cancer risk, including that of lung, colorectal, bladder, and prostate cancer.

Seventeen studies of IL-8-251 polymorphism, two of IL-6+396, and two of IL-6+781 in relation to the development of gastric cancer and peptic ulcer have appeared. Of these, six studies have shown a significantly increased risk of gastric cancer for the IL-8-251 A/A high producer genotype or A allele carriers, while four have shown an increase for peptic ulcer and one for gastric mucosal atrophy. The IL-8-251 A/A genotype is more common in Asians than Caucasians, the difference in the prevalence between Asian and Western countries.

On combined analysis, IL-6-174, IL-6-597 and IL-6+643 polymorphisms have shown no significant relationship with gastric disease. When patients are divided into Asian and Western populations, however, a clear difference in the prevalence of IL-6-572 genotypes is seen. The risk of gastric non-cardia cancer and peptic ulcer development in Western populations was 21.13 (95% CI: 5.56-131.98) and 2.98 (1.05-8.47) for the C/G and G/G genotypes, respectively (Table 8). In contrast, no significant differences have been seen between Asian and gastric cancer or NUD.

This influence of the IL-6-174 and IL-6-572 polymorphisms on disease development may have been due to geographic differences. Furthermore, the influence of IL-4-590 polymorphism on gastroduodenal diseases is particularly strong in Western populations.

### Table 9 ORs for the development of gastric non-cardia cancer with the IL-6-174, +572, +597 and +634 polymorphisms

| Genotype | 1NUD (n) | Cancer (n) | OR | 95% CI | P value | Ulcer (n) | OR | 95% CI | P value |
|----------|----------|------------|-----|--------|---------|-----------|-----|--------|---------|
| IL-6-174 |          |            |     |        |         |           |     |        |         |
| C/C      | 126      | 34         |     |        |         | 1         |     |        |         |
| C/G      | 310      | 82         | 0.98| 0.63-1.54| 0.93    | 26        | 10.57| 1.42-78.73| 0.02    |
| G/G      | 261      | 142        | 2.02| 1.31-3.10| <0.01   | 124       | 59.86| 8.27-433.4| <0.01   |
| G carrier| 571      | 224        | 1.45| 0.97-2.19| 0.06    | 150       | 33.10| 4.59-238.8| <0.01   |
| IL-6+572 |          |            |     |        |         |           |     |        |         |
| C/C      | 177      | 173        |     |        |         | 1         |     |        |         |
| C/G      | 143      | 143        | 1.02| 0.75-1.40| 0.89    | 214       | 0.81 | 0.61-1.07| 0.15    |
| G/G      | 20       | 29         | 1.48| 0.81-2.72| 0.20    | 44        | 1.19 | 0.68-2.08| 0.54    |
| G carrier| 163      | 172        | 1.08| 0.80-1.46| 0.61    | 258       | 0.86 | 0.66-1.12| 0.26    |
| IL-6+597 |          |            |     |        |         |           |     |        |         |
| G/G      | 102      | 75         |     |        |         | -         |     |        |         |
| G/A      | 102      | 67         | 0.89| 0.58-1.37| 0.61    | -         |     |        |         |
| A/A      | 61       | 28         | 0.62| 0.37-1.07| 0.09    | -         |     |        |         |
| A carrier| 163      | 95         | 0.79| 0.54-1.17| 0.24    | -         |     |        |         |
| IL-6+634 |          |            |     |        |         |           |     |        |         |
| C/C      | 118      | 96         |     |        |         | -         |     |        |         |
| C/T      | 84       | 55         | 0.81| 0.52-1.24| 0.33    | -         |     |        |         |
| T/T      | 9        | 4          | 0.45| 0.16-1.83| 0.32    | -         |     |        |         |
| T carrier| 93       | 59         | 0.79| 0.51-1.12| 0.25    | -         |     |        |         |

1NUD includes patients with gastritis without gastric cancer and peptic ulcer, and atrophic gastritis. Because we deleted a number of gastric cardia cancer patients, the number of cancer patients shown in this Table does not match that in Table 3.
Table 10  ORs for the development of gastric non-cardia cancer with IL-8-251, +396 and +781 polymorphisms

| Genotype | NUD (n) | Cancer (n) | OR | 95% CI | P value | Ulcer (n) | OR | 95% CI | P value |
|----------|---------|------------|----|--------|---------|-----------|----|--------|---------|
| IL-8-251 |         |            |    |        |         |           |    |        |         |
| T/T      | 2000    | 978        | -  |        |         | 370       |    |        |         |
| T/A      | 2518    | 1244       | 1.01 | 0.91-1.12 | 0.38    | 532       | 1.14 | 0.99-1.32 | 0.07   |
| A/A      | 892     | 401        | 0.92 | 0.80-1.06 | 0.24    | 163       | 0.99 | 0.81-1.21 | 0.90   |
| A carrier | 3410    | 1645       | 0.99 | 0.90-1.09 | 0.18    | 695       | 1.10 | 0.96-1.26 | 0.17   |
| IL-8+396 |         |            |    |        |         |           |    |        |         |
| T/T      | 224     | 27         | -  |        |         | -         |    |        |         |
| T/G      | 293     | 43         | 1.22 | 0.73-2.03 | 0.44    | -         | -   |        |         |
| G/G      | 93      | 12         | 1.07 | 0.52-2.20 | 0.85    | -         | -   |        |         |
| G carrier | 385     | 55         | 1.18 | 0.73-1.93 | 0.50    | -         | -   |        |         |
| IL-8+781 |         |            |    |        |         |           |    |        |         |
| C/C      | 248     | 29         | -  |        |         | -         |    |        |         |
| C/T      | 282     | 41         | 1.24 | 0.75-2.06 | 0.39    | -         | -   |        |         |
| T/T      | 84      | 11         | 1.12 | 0.54-2.34 | 0.76    | -         | -   |        |         |
| T carrier | 366     | 52         | 1.22 | 0.75-1.97 | 0.43    | -         | -   |        |         |

NUD includes patients with gastritis without gastric cancer and peptic ulcer, and atrophic gastritis. Because we deleted a number of gastric cardia cancer patients, the number of cancer patients shown in this Table does not match that in Table 4.

Figure 1  Scheme of the association of inflammatory cytokine polymorphisms and gastroduodenal disease development.

**Summary of association between H. pylori-related diseases and cytokine polymorphisms**

In general, gastric mucosal inflammation in *H. pylori* infection of gastric mucosa is exacerbated in patients with high producer alleles of pro-inflammatory cytokines and low producer alleles of anti-inflammatory cytokines, which results in a higher risk for the development of gastric cancer and gastric ulcer (Figure 1). In contrast, low producer allele carriers of pro-inflammatory cytokines and high producer allele carriers of anti-inflammatory cytokines have mild gastric mucosal inflammation (Figure 1). A summary of the association between *H. pylori*-related diseases and cytokine polymorphisms is shown in Table 11. As important points, the prevalence of cytokine gene genotypes differs between Western and Asian populations. Although Asian populations have been reported to be associated with more severe neutrophil infiltration in non-cancerous gastric mucosa adjacent to cancer. These results may be due to the tumorigenic and angiogenic functions of IL-8 modulating the growth and invasive behavior of malignant tumors by autocrine and paracrine mechanisms, and suggest that genetic variants of IL-8 potentially affect the prognosis of gastric cancer. Nevertheless, several contrary studies have also appeared. Lee et al.[96,100-102] have reported that the prevalence of *H. pylori*-related diseases and cytokine polymorphisms has no significant relationship with the incidence of gastric disease (Table 10). However, the prevalence of *IL-8*-251 polymorphisms differs between Western and Asian populations (Table 7), and the risk for peptic ulcer in Western populations is higher [1.53 (1.09-2.14) for the *IL-8*-251 A/A genotype and 1.49 (1.14-1.96) for A allele carriers] (Table 8). The *IL-8*-251 polymorphism more potentially influences the development of peptic ulcer in Western than East Asian populations.

In combined analysis, the *IL-8*+396 and *IL-8*+781 polymorphisms have no significant relationship with the risk of gastric cancer development (Table 10). However, Savage et al.[98,100] have reported that the *IL-8*-251/ +396/+781 AGT/AGC haplotype is associated with a fourfold increased risk of gastric cancer. This haplotypic analysis will help identify groups with a higher risk of disease and should be investigated in a larger study.

**Figure 1  Scheme of the association of inflammatory cytokine polymorphisms and gastroduodenal disease development.**

H. pylori

- Inflammatory cytokines

  - Pro-inflammatory cytokine: High producer genotype
  - Anti-inflammatory cytokine: Low producer genotype

  - Enhanced inflammation
  - Atrophic gastritis
  - Gastric cancer

  - Suppressed inflammation
  - Antrum predominant gastritis

  - Weak acid inhibition

- Duodenal ulcer

- Increased type

- Inflammation decreased type

- Potent acid inhibition

- Potent acid inhibition

- Disease process will help identify groups with a higher risk of disease and should be investigated in a larger study.
with IL-1B-511, IL-10, TNF-α polymorphisms and development of peptic ulcer and gastric cancer,[3,19] the influence of IL-4, -6 and -8 polymorphisms on the diseases in the current review may be lower. In Western studies, combination analysis of several cytokine gene genotypes is related to development of diseases.[10] As shown in Table 11, because IL-4-590, IL-6-174, IL-6-572 and IL-8-251 polymorphisms in Western populations relate to development of gastroduodenal diseases, combination analysis including these gene polymorphisms with previously reported IL-1 and TNF-α is expected to increase detection of elevated risk of diseases. These findings should be further evaluated in a larger population.

**CONCLUSION**

Many genetic factors are associated with the development of _H. pylori_-related diseases. Of these, we have reviewed here the important role of inflammatory cytokines (IL-2, IL-4, IL-6 and IL-8) and their polymorphisms in _H. pylori_-related diseases. We recommend intensive endoscopic screening and/or eradication therapy for patients at higher risk of gastric cancer based on genetic inflammatory cytokine polymorphisms, albeit that we are unsure whether all factors should be determined. Further data to refine this recommendation are therefore required.

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