

Role of Cytokine Polymorphisms in the Risk of Distal Gastric Cancer Development

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Abstract

We review the current information concerning the role of cytokine polymorphisms and the risk of develop distal gastric cancer in different populations. We have included populations colonized with *Helicobacter pylori* as well as populations without colonization. We found that the study of polymorphisms alone seems insufficient to assess

gastric cancer risk and it is necessary to examine environmental factors in different ethnic groups and geographic areas along with the study of *H. pylori* strains to define better the risk factors associated with distal gastric cancer. (Cancer Epidemiol Biomarkers Prev 2005;14(8):1869–73)

Introduction

Stomach cancer was the most common form of cancer in the world in the 1970s and early 1980s and is now surpassed only by lung cancer. The incidence of gastric cancer shows marked variation among countries in the world (1). Incidence rates are especially high in Japan and other Eastern Asian countries; other areas in the world, including Eastern Europe and parts of Latin America (2), have high incidence rates of gastric cancer as well.

Gastric cancer is a multifactorial disease. Mortality rates for this cancer worldwide have been declining for several decades (3). Despite the decline in distal gastric cancer in many countries of the world, it remains a major public health problem. The number of new cases in the elderly population of both developed and developing countries is rising. It is estimated that more than a million cases per year will occur in the next 10 years (1).

Since 1991, epidemiologic evidence has shown that gastric cancer is associated with *Helicobacter pylori* colonization (4). However, many studies have shown that even through certain region of the world where nearly 100% of the persons are colonized with *H. pylori* the risk of developing gastric cancer is not as high as expected, particularly in sub-Saharan Africa and Southeast Asia (5). Bacterial virulence factors such as the *cag* pathogenicity island, the vacuolating cytotoxin, and others have been associated with higher risk for gastric cancer development particularly in western countries but these associations are less relevant in countries including east Asia and developing countries (6, 7).

Host genetic factors are emerging as determinants of increasing risk for many cancers (8, 9). Cytokines participate in the inflammatory response associated with innate immunity and the acquired immune response. Cytokines such as INF γ , interleukin-1 β (IL-1 β), and tumor necrosis factor- α (TNF- α) are up-regulated during *H. pylori* infection. Genes encoding cytokines and related molecules harbor polymorphic regions, which alter gene transcription and thereby influence inflammatory processes in response to infectious disease (10). Polymorphisms in human *IL-10*, *IL-1B*, *TNF-A*, *IFN-G*, and

IL-1 receptor antagonist (*IL-1RN*) genes have been reported to influence cytokine expression. In gastric cancer, several cytokine polymorphisms, such as IL-1 β , IL-10, TNF- α , and others, have been evaluated as risk factors.

IL-1 encompasses a cluster of genes located on chromosome 2q, the products have an important role in controlling inflammatory response as well as controlling the acidity of the stomach (11). The cluster contains three related genes *IL-1A*, *IL-1B*, and *IL-1-RN*, which encode the proinflammatory cytokines IL-1 α , IL-1 β , and their endogenous receptor antagonist IL-1ra, respectively (11).

IL-1B

Two diallelic polymorphisms in *IL-1B* have been reported (Fig. 1), each one representing C-T base transitions at positions -511 and -31. IL-1 β is up-regulated in the presence of *H. pylori* and is important in initiating and amplifying the inflammatory response to this infection. IL-1 β is also a potent inhibitor of gastric acid secretion (12). A biallelic polymorphism at positions -31 and -511 in the promoter of the *IL-1B* gene have been associated with the development of gastric cancer and its precursors (Table 1; refs. 13-16).

IL-1RN

The *IL-1RN* gene has a penta-allelic 86-bp variable number tandem repeat in intron 2, of which allele 2 (*IL-1RN*2*) is associated with a wide range of chronic inflammatory and autoimmune conditions and enhanced IL-1 β secretion (Fig. 2). The alleles 1, 2, 3, 4, and 5 in *IL-1 RN* gene, represent four, two, five, three, and six repeats of the 86-bp tandem repeat (see Fig. 2). As described below, the presence of allele 2 has been associated with increased risk of distal gastric cancer and its precursors (14, 15, 17, 18).

Interactions of IL-1 Polymorphisms and Gastric Cancer

The first indication of *IL-1* polymorphisms and their association with increased risk for gastric cancer was reported by El-Omar et al. (11). El-Omar et al. recently reported that functional polymorphisms in the genes for IL-1 β and its endogenous receptor antagonist (*IL-1RN*) were

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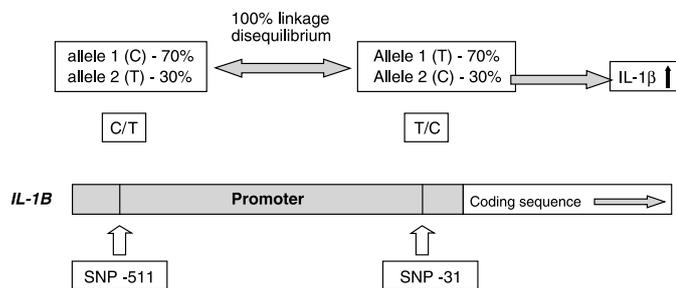


Figure 1. Schematic illustration of polymorphisms in the *IL-1B* gene. Allele frequencies of the single-nucleotide polymorphisms (SNP) in the promoter region of the *IL-1B* gene at positions -511 and -31. SNP -511T (associated with higher IL-1 β secretion) is in complete linkage disequilibrium with -31C. From an eastern European population (19).

associated with increased risk of gastric cancer and its precursors (11, 13). They found also that those polymorphisms were associated with hypochlorhydria. Furthermore, the authors noted that *IL-1B* -31 and -511 were in almost complete linkage disequilibrium.

Studies from Portugal later confirmed and extend the observations. *IL-1B* -511*T carriers who were also homozygous for the short allele of *IL-1RN* 2/2 had an increase gastric carcinoma risk [odds ratio (OR), 3.3; 95% confidence interval (95% CI), 1.3-8.2]. The authors also found that patients with greater risk for gastric carcinoma were those carrying both bacterium and host high-risk genotypes (15). In a second Portuguese study, the authors found that for chronic atrophic gastritis and gastric cancer, the odds of developing disease increased with the number of risk genotypes (17). These studies show that the combination of bacteria and host genotypes can be useful in defining a specific genetic profile associated with high risk for gastric cancer.

The carriage of multiple proinflammatory polymorphisms confers greater risk for the development of distal gastric cancer. This was recently confirmed by El-Omar et al. (12) in a study in which the ORs (95% CIs) increased from 2.8 (1.6-5.1) for one, 5.4 (2.7-10.6) for two, and 27.3 (7.4-99.8) for three or more high-risk genotypes. The same synergistic effect of *H. pylori* virulence factors and *IL-1* polymorphisms was reported in association with the development of severe histologic changes in the gastric mucosa in German patients (19).

The association of *IL-1B* gene polymorphism and gastric cancer was investigated in high- and low-prevalence regions in China (20). The authors found that *IL-1B* -511 polymorphism was associated with gastric cancer. This association was less obvious in areas of high prevalence of *H. pylori* and consequently more gastric cancer. A study from Taiwan has confirmed this observation (21). The study in China did not find complete linkage disequilibrium between *IL-1B* -511 and -31. The same observation has been reported in a study

Table 1. *IL-1* genotype frequencies (%) in gastric cancer and controls

Locus	Genotype	Cases (n = 366)	Controls (n = 429)	OR (95% CI)
<i>IL-1B</i> -31	T/T	35.0	51.0	1.0
	T/C	47.0	38.3	1.8 (1.3-2.4)
	C/C	18.0	10.7	2.5 (1.6-3.8)
<i>IL-1B</i> -511	C/C	34.7	50.6	1.0
	C/T	46.4	39.7	1.8 (1.3-2.4)
	T/T	18.9	10.7	2.6 (1.7-3.9)

NOTE: Modified from ref. 11.

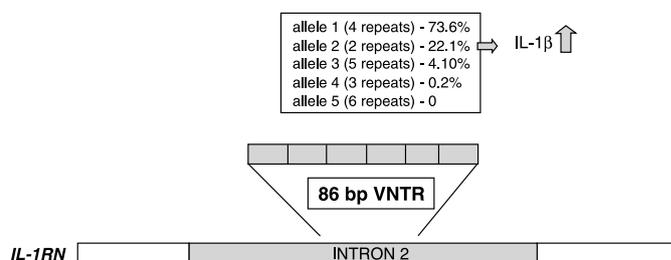


Figure 2. *IL-1RN* gene has a penta-allelic 86-bp variable number tandem repeat in intron 2, of which the allele 2 (*IL-1RA*2*) had been associated with enhanced IL-1 β production. Relative frequencies are indicated for each allele. From an eastern European population (19).

from Korea (22). In contrast, there are some studies that report a lack of association between *IL-1B* polymorphisms and gastric cancer. Lee et al. (22) in Korea did not find any association between *IL-1B* -31 or *IL-1RN*2* polymorphisms and increased risk of gastric cancer. Matsukara et al. (18) reported an ethnic difference in the association between the *IL-1B* polymorphism and gastric atrophy. In the same report, there was no association of the *IL-1B* polymorphism and the risk of gastric atrophy in Thai and Vietnamese patients.

Interactions of IL-1B Polymorphisms with Other Diseases

The *IL-1B* polymorphisms -511 and *IL-1RN* 2/2 have been associated with esophagitis in patients who are not colonized with *H. pylori*. Koivurova et al. (23) reported that the simultaneous carriage of those two polymorphisms is significantly associated with esophagitis. Garcia-Gonzalez et al. (24) confirmed that the same *IL-1B* and *IL-1RN* polymorphisms that are associated with high risk of distal gastric adenocarcinoma are associated with a reduced risk of duodenal ulcer.

Tumor Necrosis Factor- α

TNF- α is one of the proinflammatory cytokines highly expressed in *H. pylori* gastritis and a potent inhibitor of gastric acid secretion (25, 26). Although several polymorphisms have been reported in the *TNF-A* promoter, the majority of studies have been focused on the G/A polymorphism at position -307 (Fig. 3), because most of the other polymorphisms are functionally silent. Several studies found a higher concentration of TNF- α in patients with the polymorphism at position -307 with malignant tumors (27, 28).

As noted above, TNF- α is a proinflammatory cytokine, which is a mediator of the immune response in *H. pylori* and

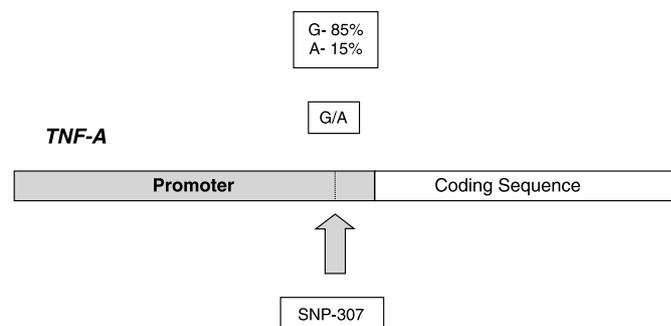


Figure 3. Schematic illustration of *TNF-A* polymorphism. Allele frequencies from an eastern European population.

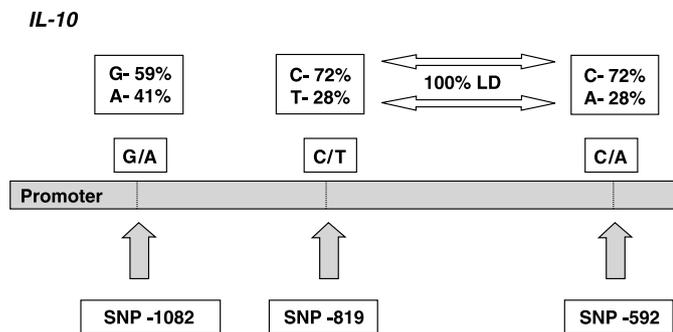


Figure 4. Schematic illustration of *IL-10* polymorphisms. Allele frequencies from German and southern European populations.

shares many biological activities with IL-1 (26). Apparently, the TNF region is crucial in the complex genetic predisposition to *H. pylori* colonization in certain patient subgroups. Kunstmann et al. (29) reported that *TNF-A* -307 wild type is associated with duodenal ulcer in female patients independent of *H. pylori* status. The functional promoter polymorphism in this gene not only plays an important role in *H. pylori*-induced gastritis but also doubles the risk of non-cardia gastric cancer without any association with the risk of esophageal or cardia gastric cancer (12). Almost identical results were reported by Machado et al. (17). The authors found that carriers of *TNF-A* -307A* allele have an increased risk of gastric cancer with an OR of 1.9 (95% CI, 1.3-2.7).

In contrast, some studies did not find an association between *TNF-A* -307 polymorphism and gastric cancer. Zamboni et al. (30) in Italy studied 210 controls and 475 patients with esophageal or gastric cancer. Their results suggested that *TNF-A* -307 might be involved in favoring *H. pylori* infection and the inflammatory response of the infected gastric mucosa but not favoring precancerous intestinal metaplasia or non-cardia gastric cancer. A recent report from Korea also indicated that not only *TNF-A* -307 but also four other polymorphisms (-1031, -863, -857, and -238) have no association with gastric cancer (31). The differences in polymorphism profile were not statistically significant between gastric cases and controls.

Whereas in some *in vitro* studies, allele A of this single nucleotide polymorphism was associated with heightened TNF- α secretion, other studies did not find such a correlation. Rad et al. (32) studied the influence of the *TNF-A* -307 polymorphism on mucosal cytokine expression and they show no significant differences in TNF- α level between different allele carriers. These results suggest that this polymorphism may not influence cytokine expression. However, it is important to extend the number of studies in this area to confirm or refute these findings.

Table 2. Frequencies (%) and age-, sex-, and race-adjusted ORs for the association of inflammatory polymorphisms in *IL-1B*, *IL-1RN*, *IL-10*, and *TNF-A* with non-cardia gastric cancer

Polymorphisms	Cases (n = 188)	Controls (n = 210)	OR (95% CI)
0	11.7	35.7	1.0
1	39.4	40.5	2.8 (1.6-5.1)
2	33.0	21.9	5.4 (2.7-10.6)
3	14.9	1.9	26.3 (7.1-97.1)
4	1.0	0.0	∞ (undefined)

NOTE: Modified from ref. 12.

Table 3. Estimated ORs for the association of cytokine polymorphisms in seropositive patients to *H. pylori* and CagA antigen preparations

Polymorphism	<i>H. pylori</i> ⁺	CagA ⁺
<i>IL-1B</i> -511*T	4.2	9.9
<i>IL-1RN</i> *2*2	1.6	2.9
<i>IL-10</i> ATA/ATA	2.9	5.2
<i>TNF-A</i> -308*A	2.9	6.2

IL-10

Inflammatory reactions are an essential component of host defense mechanisms, but prolonged or excessive inflammation is deleterious; therefore, the inflammatory process must be tightly regulated. The key regulators of inflammation are the cytokines, proinflammatory (IL-1 β and TNF- α) and the anti-inflammatory (IL-10). The possible roles of proinflammatory cytokine in gastric cancer were noted above; anti-inflammatory cytokines also play a role. In the *IL-10* gene promoter, single nucleotide polymorphisms at positions -1082 (G/A), -819 (C/T), and -592 (C/A) have been reported to produce three main haplotypes: GCC, ACC, and ATA (refs. 9, 32; Fig. 4).

Rad et al. (32) have recently shown that carriers of the *IL-10* -1082G, -819C, and -592C alleles had higher mucosal *IL-10* mRNA than ATA haplotype carriers. These results confirmed the relevance of *IL-10* polymorphisms in the down-regulation of the inflammatory response. El-Omar et al. have recently reported that certain polymorphisms in anti-inflammatory cytokine genes, such as *IL-10*, were associated with more than doubling of the risk of non-cardia gastric cancer (12). Patients homozygous for the hypoactive *IL-10* alleles *IL-10* -1082A and *IL-10* -592A, as well as for the "low *IL-10*" haplotype ATA (*IL-10* -1082A, *IL-10* -819T, and *IL-10* -592A) had significantly increased risks of non-cardia gastric cancer.

Garza-Gonzalez et al. (33) studied the potential role of *IL-10* polymorphisms in gastric cancer patients. They found no association between *IL-10* polymorphisms (-592 and -1082) and gastric cancer in a very small study (33 gastric cancer cases and 25 controls).

Association Between Multiple Polymorphisms and Gastric Cancer Risk

The combination of multiple proinflammatory polymorphisms and some anti-inflammatory polymorphisms conferred greater risk for gastric cancer as illustrated in Table 2 (12). The association of *IL-10*, an anti-inflammatory cytokine, with proinflammatory cytokines such as IL-1 β and TNF- α may be explained by the role of *IL-10* in down-regulating the proinflammatory cytokines. In addition, some reports suggest an important role for cytokine expression in the level of the inflammatory response observed *in vivo* (34).

In contrast, the number of inflammatory cytokine polymorphisms was not statistically significantly associated with

Table 4. *H. pylori* and CagA status-adjusted ORs for the association of inflammatory polymorphisms with non-cardia gastric cancer

No. polymorphism	<i>H. pylori</i> ⁺	CagA ⁺
1	5.4	6.6
2	8.3	19.5
3	42.0	∞ (undefined)

Table 5. Combination of *H. pylori* and *IL-1B* genotype in non-atrophic gastritis and non-cardia gastric cancer patients

<i>H. pylori</i> and <i>IL-1B</i> -511	NAG	NCGC	OR (95% CI)	P
<i>vacA</i> S2/C homozygote	27	1	1 (reference)	
<i>vacA</i> S2/T homozygote	35	8	6.2 (0.7-52)	0.1
<i>vacA</i> S1/C homozygote	17	27	43 (5.3-345)	<0.001
<i>vacA</i> S1/T homozygote	22	71	87 (11-679)	<0.001
<i>cagA</i> -/C homozygote	35	4	1 (reference)	
<i>cagA</i> -/T homozygote	46	8	1.5 (0.4-5.5)	0.52
<i>cagA</i> +/C homozygote	26	38	13 (4.1-40)	<0.001
<i>cagA</i> +/T homozygote	28	80	25 (9.2-77)	<0.001

the risk of esophageal squamous cell carcinoma, adenocarcinoma of the esophagus, or gastric cardia cancer. ORs for carriage of three or four inflammatory genotypes were 0 (95% CI, 0-10.5), 1.3 (95% CI, 0.2-8.0), and 3.6 (95% CI, 0.8-16.7), respectively.

Other cytokine polymorphisms have been recently described, including *IL-8* -251, Thr³⁹⁹Ile, and *TLR-4* Asp²⁹⁹Gly and are currently under study for their role in cytokine level and cancer risk.

Effect of Cytokine Polymorphisms and *H. pylori* Status

An interesting finding in the El-Omar study (12) was the association between cytokine polymorphisms and *H. pylori*-seropositive status. Tables 3 and 4 show clearly that the ORs are higher in *H. pylori*- and CagA-positive patients than in the whole population studied in Table 2. This observation has been confirmed in patients with severe histologic changes in the gastric mucosa (20).

The study of Figueiredo et al. (15) is probably the most complete study that shows that the pattern of bacterial and host genotypes may determine risk of developing distal

Table 6. Summary of the role of cytokine polymorphisms in the development of upper gastrointestinal pathologies

Reference	Studied population	Ethnicity	Cytokine polymorphism	Finding
(29)	209 <i>H. pylori</i> ⁺ , 184 <i>H. pylori</i> ⁻	Caucasian (German)	<i>TNF-A</i> -308 G/G	Risk factor for duodenal ulcer in <i>H. pylori</i> ⁺ females
(11)	393 cases, 430 controls	Caucasian (Americans)	Haplotype <i>IL-1B</i> -31C/ <i>IL-1RN</i> *2	Increased risk of gastric cancer
(17)	152 cases, 218 controls	Portuguese	<i>IL-1B</i> -511T+ <i>IL-1RN</i> *2/*2	Increased risk for gastric carcinoma and synergistic interaction between both polymorphisms.
(13)	579 <i>H. pylori</i> ⁺ , 227 <i>H. pylori</i> ⁻	Asian (Japanese)	<i>IL-1B</i> -511 T/T	Associated with atrophic gastritis
(15)	221 chronic gastritis, 222 gastric carcinoma	Portuguese	<i>IL-1B</i> -511T+	Patients with greater risk for gastric carcinoma were those with both bacterial (<i>cagA</i> ⁺ / <i>vacAs1</i> ⁺) and host high-risk genotypes.
(16)	117 <i>H. pylori</i> ⁺ CagA ⁺ patients	Asian (Japanese)	<i>IL-1B</i> -511 T/T	Higher mucosal <i>IL-1β</i> levels
(19)	210 <i>H. pylori</i> ⁺	Caucasian (German)	<i>IL-1RN</i> *2 <i>IL-1B</i> -511T/-31C	Increased risk for the development of atrophic gastritis, intestinal metaplasia, and severe inflammation.
(12)	188 cases, 210 controls	Caucasian (Americans)	<i>IL-1B</i> -511T+ <i>IL-1RN</i> *2/*2 <i>IL-10</i> ATA/ATA <i>TNF-A</i> -308A+ <i>IL-1B</i> -511	Higher prevalence if host is colonized with bacterial high-risk genotypes (<i>cagA</i> ⁺ / <i>vacAs1</i> ⁺) as well. The carriage of multiple proinflammatory polymorphisms confers greater risk for the development of gastric cancer.
(18)	646 patients with various gastrointestinal complaints	Asian (Japanese, Chinese, Vietnamese, Thai)	<i>IL-1B</i> -511	No association of the <i>IL-1β</i> polymorphism and the risk of gastric atrophy in Thai and Vietnamese patients.
(20)	86 cases, 169 controls	Asian (Chinese)	<i>IL-1B</i> -511 T/T	Associated with gastric cancer
(22)	190 gastric cancer, 117 duodenal ulcer, 172 controls	Asian (Korean)	<i>IL-1B</i> -31C+ <i>IL-1RN</i> *2/*2	Lack of association with an increase in risk of gastric cancer and duodenal ulcer
(33)	33 cases, 25 controls	Hispanic (Mexican)	<i>IL-1B</i> -31C+ <i>IL-1RN</i> <i>IL-10</i> (-592, 1082) <i>TNF-A</i>	Associated with increased risk of gastric cancer No association
(30)	129 gastric cancer, 792 upper gastrointestinal pathologies	Caucasian (Italians)	<i>IL-1B</i> -31	Failed to find association with increased risk of gastric cancer or its precursors
(21)	142 cases, 164 controls	Asian (Chinese)	<i>IL-1B</i> -511 <i>IL-1RN</i> *2	No difference between cases and controls First study to verify association with development of gastric cancer in Asian individuals.
(31)	341 gastric cancer, 133 duodenal ulcer, 261 controls	Asian (Korean)	<i>TNF-A</i> (-308, -1031, -863, -857, -238)	No association with gastric cancer
(32)	207 <i>H. pylori</i> ⁺ , 535 <i>H. pylori</i> ⁻	Caucasian (89% German)	<i>IL-1B</i> -511T+ <i>IL-1RN</i> *2 <i>IL-10</i> GCC <i>IL-10</i> ATA <i>TNF-A</i>	Associated with increased mucosal <i>IL-1β</i> expression and prevalence of atrophic gastritis. Higher mucosal <i>IL-10</i> mRNA levels Colonization by more virulent <i>H. pylori</i> strains No influence on mucosal cytokine expression

gastric cancer (Table 5). Bacterial status and genotype were determined by PCR and not by serology. The study concentrated on two of the major virulence factors in *H. pylori*, *vacA* and *cagA*. In particular, the authors were able to assess the s1 and m1 regions of *vacA* that have been associated with the most severe *H. pylori*-related disease outcome. Overall, the findings suggest that it is possible to define a disease risk profile combining host and bacterial genotypes in distal gastric cancer, which may be useful in prevention programs.

Table 6 summarizes the association of different cytokine polymorphisms, *H. pylori* carriage, and gastric pathologies.

Conclusions

It is clear that colonization with *H. pylori* increases the risk of developing distal gastric cancer and perhaps there are further additive effects on risk if specific host cytokine polymorphisms coincide with specific bacterial genotypes. We have presented some of the most recent evidence for these associations. Furthermore, the combination of more virulent *H. pylori* strains and the expression of specific cytokine polymorphisms contribute to an increasing risk of developing distal gastric cancer. We have mentioned that there is a need for more studies in different geographic regions of the world and in a wide diversity of ethnic populations to explore whether colonization with virulent *H. pylori* strains and expression of cytokine polymorphisms contribute to an increased risk of developing distal gastric adenocarcinoma. As Furuta et al. mentioned in a recent editorial (35), the study of polymorphisms alone seems insufficient to assess gastric cancer risk and they suggest examining environmental factors in different ethnic groups and geographic areas along with the study of *H. pylori* strains. Studies of this type may be required to determine the most important risk factors associated with distal gastric cancer in a particular region of the world.

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