Human Genome Epidemiology (HuGE) Review

Polymorphisms in Inflammatory Response Genes and Their Association With Gastric Cancer: A HuGE Systematic Review and Meta-Analyses

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To evaluate the association between gastric cancer susceptibility and inflammation-related gene polymorphisms, the authors conducted a series of meta-analyses using a predefined protocol. Genes investigated were those coding for the interleukin (IL) proteins (IL1B, IL1RN, IL8, and IL10) and for tumor necrosis factor-alpha. Gastric cancers were stratified by histologic subtype and anatomic subsite, by Helicobacter pylori infection status, by geographic location (Asian or non-Asian study population), and by a quantitative index of study quality. All published literature and meeting abstracts from the period 1990–2006 were considered. Results consistently supported increased cancer risk for IL1RN2 carriers; the increased risk was specific to non-Asian populations and was seen for intestinal and diffuse cancers, distal cancers, and, to a lesser extent, cardia cancers. Analyses restricted to high-quality studies or H. pylori-positive cases and controls also showed significant associations with both carrier status and homozygosity status. In Asian populations, reduced risk was observed in association with IL1B-31C carrier status. This effect was also observed in analyses restricted to high-quality studies. These results indicate the importance of stratification by anatomic site, histologic type, H. pylori infection, and country of origin. Study quality considerations, both laboratory and epidemiologic, can also affect results and may explain, in part, the variability in results published to date.

epidemiology; genetics; Helicobacter pylori; interleukins; meta-analysis; polymorphism, genetic; stomach neoplasms

Abbreviations: IL, interleukin; OR, odds ratio; SNP, single nucleotide polymorphism; TNF, tumor necrosis factor.

Editor’s note: This article also appears on the Web site of the Human Genome Epidemiology Network (http://www.cdc.gov/genomics/hugenet/default.htm).

DISEASE–GENE ENVIRONMENT

Gastric cancer is a major contributor to cancer-related death worldwide. Although gastric cancer incidence and mortality have declined in most areas of the world, gastric cancer is still the fourth most common cancer in the world and, because of its poor prognosis, the second most common cause of cancer-related death (1). The Gram-negative bacterium Helicobacter pylori is a well-established etiologic factor and has been classified as a class 1 carcinogen because of its causative role in the development of gastric cancer (2). The ability of H. pylori to infect and live persistently in the human stomach elicits a chronic inflammatory response, which may be of variable magnitude depending on the host’s genetic makeup. Differing inflammatory responses among hosts may help to explain different outcomes for persons infected with H. pylori. Therefore, polymorphisms present in genes involved in the host inflammatory response to this infection may alter susceptibility to gastric cancer.

GENE VARIANTS AND FUNCTION

Many investigators have reported associations between single nucleotide polymorphisms (SNPs) in genes that
regulate the host’s inflammatory response and gastric cancer, with sometimes conflicting results. The inflammatory-response-related genes that have been most frequently studied in relation to gastric cancer are interleukin (IL) genes IL1B, IL1RN, IL8, and IL10 and tumor necrosis factor-alpha (TNFA), coding for the proteins IL-1β, IL-1ra, IL-8, IL-10, and TNF-α, respectively. These cytokines are important mediators in gastric physiology and pathophysiology and could play important roles in the etiology of gastric cancer (e.g., IL-1 controls stomach acidity, IL-8 stimulates the proliferation of endothelial cells, IL-10 down-regulates cytotoxic responses, and the proinflammatory cytokine TNF-α mediates inflammatory responses). Most of the SNPs studied here (see Web Table 1, which is posted on the Journal’s Web site (http://aje.oxfordjournals.org/)) are situated in the gene promoter region and play important roles in modulating gene expression and thus the inflammatory response. An earlier study based upon a transgenic mouse model demonstrated that elevation in the level of a single proinflammatory cytokine, IL-1β, is enough to induce gastric dysplasia or carcinogenesis, through the pathways of IL-1β, IL1-R1, and NF-kB (nuclear factor-κ-light-chain-enhancer of activated B cells). In this model, IL-1β activates myeloid-derived suppressor cells in the stomach, whose mobilization and recruitment correlate with increased levels of IL-6 and TNF-α in serum and the stomach. Furthermore, the myeloid-derived suppressor cells also inhibit T- and B-cell proliferation. This provides a direct link between IL-1β, the myeloid-derived suppressor cells, and carcinogenesis via stepwise spontaneous inflammation, metaplasia, and dysplasia (3).

We conducted a series of meta-analyses, using a predefined protocol, to estimate the relation between gastric cancer and polymorphisms in the inflammatory-response-related genes that have been most frequently investigated. The meta-analyses were stratified by anatomic site, histologic type, and geographic location (Asian vs. non-Asian populations), as well as by study quality criteria. Unlike previously published meta-analyses (4–9), we also stratified by H. pylori infection status and imposed no language limitations in our selection criteria. Further, we contacted authors of all papers for which data were incomplete or had been published only in abstract form.

MATERIALS AND METHODS

A written protocol (available on request) with predefined inclusion criteria and bibliographic search terms was developed and was used for all subsequent procedures.

Search strategy

We constructed a list of search terms, including words associated with or synonymous with the search terms: “gastric cancer” and “IL-1B,” “IL-1RN,” “IL-8,” “IL-10,” “TNF-alpha” and “polymorphisms.” We conducted a pilot study to establish whether these terms were sufficiently comprehensive or needed modification; simultaneously, we evaluated the proposed data extraction sheets. After modification, the main search was conducted (available on request), identifying all published literature and meeting abstracts for the period between January 1990 and April 28, 2006, in the MEDLINE, PubMed, EMBASE, Web of Science, and BIOSIS databases, with no language limitations. Citations were merged together in Reference Manager, version 11 (Thomson Research Soft, Carlsbad, California, 2005), resulting in the retrieval of 16,216 references (3,144 from MEDLINE, 3,649 from EMBASE, 2,876 from PubMed, 4,240 from BIOSIS, and 2,307 from Web of Science). Duplicates were identified through electronic title scans, resulting in 8,347 exclusions. The remaining 7,869 references were sorted into groups representing further exclusion categories (e.g., animal studies, cell-line studies, and case reports). A second investigator provided an independent review of 1,500 remaining potentially eligible references, resulting in 180 references for which the full-text article was retrieved and considered. Discrepancies between investigators were resolved through discussion.

Inclusion and exclusion criteria

The following inclusion criteria had to be fulfilled: 1) either a cross-sectional, case-control, cohort, or case-case study design; 2) data on any/some or all polymorphisms in the following genes: IL1B, IL1RN, IL8, IL10, and TNFA; 3) clear definitions of cases and controls (age, sex, case and control selection) and type or site of gastric cancer; and 4) reporting of outcomes and risk estimates and/or presentation of data necessary for calculating odds ratios and risk ratios. Excluded were: 1) case reports; 2) studies with no risk estimation or no raw data from which risk could be calculated after contacting authors; and 3) studies overlapping with other studies and studies with overlapping data from the same authors. Excluded studies are described in Web Table 2.

Data extraction

Data were extracted independently and in duplicate by 2 reviewers who used standardized data extraction forms. For each study, the following characteristics were extracted: names of authors; country of study; time of study (start date and end date); ethnic group of the study population; H. pylori-positive infection proportions in cases and controls; characteristics of gastric cancer cases (age distribution (median, mean, maximum, minimum), sex ratio, source of population (blood donors, hospital, etc.), and site/type of gastric cancer); characteristics of controls (age distribution (median, mean, maximum, minimum), sex ratio, and source of population); numbers of genotyped cases and controls; frequencies of the genotypes and/or haplotypes (wild-type pattern); genotype frequencies among H. pylori-infected persons; genotype frequencies among proximal (or cardia), distal, intestinal (or differentiated), and diffuse (or undifferentiated) types of gastric cancer; genotype frequencies among gastric cancer patients overall (including studies that both provided and did not provide information on anatomic location and histologic type); and analytic methods and study results (odds ratio, covariates used for adjustment, P values, methods used for measuring H. pylori infection status, and methods for quality control of the genotyping).
Supplementary information was obtained, when required, by contacting the studies’ authors. Initial contacts were made by e-mail and, if no reply was received within 1 month, via mail. Authors of 75 abstracts were contacted; 61 replied, though not all supplied the complete information requested (Web Table 3).

**Study quality and validation of study**

The quality of the studies was assessed by assigning a quality score using a standardized extraction form. Scores were based on both earlier scoring systems (5) and additional criteria (Web Table 4). The total score ranged from 0 (lowest) to 20 (highest quality). We stratified our analyses according to study quality. Four studies (10–13) included either data from different geographic regions or data from more than 1 population, and we considered each region or population as a separate study.

**Statistical analysis**

Information from the extraction forms and quality forms was entered into a database in Excel 2002 (Microsoft Corporation, Seattle, Washington) and further analyzed using Stata 9.2 (Stata Corporation, College Station, Texas). We assessed Hardy-Weinberg equilibrium for the controls in each study by the χ² goodness-of-fit test with 1 df to compare the observed and expected genotype frequencies. No value was added to cells with zero counts. For studies including subjects from different ethnic groups, *H. pylori* infection in cases and controls, anatomic location, and histologic type of gastric cancer, data were extracted separately. All odds ratios and 95% confidence intervals were recalculated from raw data, using the information from the extraction sheet or data sent by the contacted authors. Odds ratios (ORs) were estimated for the following comparisons: homozygotes versus wild type (ORHM), heterozygotes versus wild type (ORHT), and carriers (homozygotes and heterozygotes) versus wild type (ORCR).

**Meta-analysis**

For meta-analysis calculations, we included polymorphisms for which at least 5 studies provided data, using both fixed- and random-effects models (only results from random-effects models are presented here). Pooled estimates of the odds ratio and 95% confidence interval were calculated for each polymorphism, using the log odds ratio and the corresponding standard errors. Studies that included information on histologic type, anatomic location, and *H. pylori* infection allowed stratification and exploration of the impact of the polymorphisms in strata defined by these factors. We also stratified the data by geographic location (Asian vs. non-Asian) and by quality score: high-quality studies (quality score ≥15) versus lower-quality studies (quality score <15).

Heterogeneity and bias were investigated using the *I²* statistic (14). This revealed the variation across studies, where values approaching zero (0%) indicated no observed heterogeneity and larger values increasing heterogeneity. The sources of heterogeneity were investigated using sub-group analyses carried out by geographic location (Asian vs. non-Asian populations), *H. pylori* positivity in cases and controls, study quality, and site/type of gastric cancer. To evaluate publication bias, we used Begg’s and Egger’s tests (15, 16).

**RESULTS**

**Characteristics of studies**

In total, we identified 76 studies examining the relation between *IL1B*, *IL1RN*, *IL8*, *IL10*, and/or *TNFA* polymorphisms and gastric cancer risk. We included meta-analysis results for which a minimum of 5 independent studies provided data; therefore, we excluded data concerning the following SNPs: *IL8*+396, *IL8*+781, *TNFA*-1031, *TNFA*-863, *TNFA*-857, and *TNFA*-376. Because of missing information (after contact with authors or when authors did not reply), 62 studies involving 9,905 cases and 14,672 controls were used in the final analyses (Table 1). Characteristics of the studies are given in Web Table 3. Thirty-six of the studies were conducted in Asia (10, 12, 17–48), 18 in Europe (11, 13, 49–62), 1 in North America (63), and 7 in Latin America (64–70).

Because of space limitations, detailed results for all meta-analyses are presented in Web Tables 5–14. We have not referenced results from analyses with fewer than 5 studies. These results show studies stratified by geographic location (Asian vs. non-Asian) and study quality for gastric cancer overall and by subsite and subtype (including restriction to *H. pylori*-positive cases and controls), as well as estimations for carriers (ORCR) versus homozygotes (ORHM).

**Overall results for carriers of all polymorphisms**

Tables 2–6 summarize the results for gastric cancer overall and by anatomic site and histologic type. The tables show the direction of association for statistically significant associations after pooled analysis in all studies and then in all high-quality studies, as well as in Asian and non-Asian populations. Also indicated in the tables, for each association, are the number of studies and the impact of restriction to *H. pylori*-positive cases and controls.

Analysis of gastric cancer overall, without stratification by histologic type or anatomic site or by country of origin, showed statistically significant associations in *IL1RN*2 and *IL10*-592A carriers. Further significant associations were found after stratification of the studies into Asian and non-Asian populations. In studies from Asian populations, an increased risk of gastric cancer among *IL10*-1082G carriers and a decreased risk among *IL10*-31C carriers was observed. Studies from non-Asian populations showed an increased risk among *IL1RN*2 carriers and a decreased risk among *IL10*-1082G carriers (Table 2).

Anatomic site of gastric cancer. In studies from non-Asian populations, increased risks among carriers of *IL1B*-511T, *IL1B*-31C, and *IL1RN*2 for the cardia subsite of gastric cancer were observed, although none of these findings were statistically significant in Asian populations. For the distal site of gastric cancer in studies from Asian
populations, IL1B-31C carriers were found to have a decreased risk and IL1RN2 carriers an increased risk. An increased risk was also shown in carriers of the IL1B-511T, IL1RN2, and TNFA-308A alleles among non-Asian populations (Table 3 and Table 4).

Histologic type of gastric cancer. In studies reporting results for the intestinal type of gastric cancer, Asian populations showed a statistically significant decreased risk among IL1B-511T and IL1B-31C carriers and an increased risk among non-Asian IL1RN2 carriers. For studies from non-Asian populations, increased risks for IL1RN2 and TNFA-308A carriers and a decreased risk of the diffuse type of cancer among IL10-1082G carriers were found (Table 5 and Table 6).

We could not find any evidence of publication bias in the analysis of IL1B-31, IL1B-511, and IL1RN polymorphisms, but we found a tendency towards such bias in the reporting of results concerning TNFA-308 polymorphisms.

IL1B-511 polymorphism

Forty studies of the IL1B-511 polymorphism, with data from 21 Asian populations (12, 18, 19, 21-25, 28, 31, 34, 35, 37-39, 42, 44-46, 48) and 19 non-Asian populations (11, 13, 14, 49, 51, 53-60, 63, 65, 66, 68, 70), were considered (Web Table 5). The overall estimated odds ratios for gastric cancer for all studies combined were 1.07 ($I^2 = 42.0$) and 1.05 ($I^2 = 55.9$) for homozygotes and carriers (ORHM and ORCR), respectively. These odds ratios were not statistically significant.

Anatomic site of gastric cancer. Overall, there was a statistically significant effect for 11 studies reporting data on the cardia subsite (ORHM = 1.58), and the association was maintained when analysis was based on the 7 high-quality studies (ORHM = 1.62). This effect was not statistically significant for T carrier status (ORCR = 1.26 for all studies and ORCR = 1.24 for high-quality studies). However, when the 8 studies from non-Asian populations were considered specifically, statistically significant elevated odds ratios were observed for both homozygosity and carrier status (ORHM = 1.85 and ORCR = 1.36) and in analyses restricted to the 6 high-quality studies (ORHM = 1.83 and ORCR = 1.35).

On the basis of 19 studies, the overall ORHM and ORCR for the distal subsite of gastric cancer were 1.27 ($I^2 = 66.7$) and 1.25 ($I^2 = 69.3$), respectively. The latter finding was statistically significant, but the significance was not maintained among the 8 high-quality studies (ORCR = 1.30). These associations were slightly stronger in the 10 studies carried out among non-Asian populations (ORHM = 1.35 ($I^2 = 77.3$) and ORCR = 1.44 ($I^2 = 70.1$)), although, again, only the ORCR was statistically significant, and this significance was not maintained among high-quality studies.

Histologic type of gastric cancer. No statistically significant effects were found for histologic type overall. For the 9 studies from Asian populations, the IL1B-511T allele was associated with a significantly reduced risk for the intestinal type of gastric cancer in both carriers (ORCR = 0.78) and homozygotes (ORHM = 0.69). The statistical significance was not observed when analyses were restricted to high-quality studies. For the diffuse type of gastric cancer, a statistically significantly reduced odds ratio (ORCR = 0.71) was observed within high-quality studies from Asian populations, but this was based on only 3 studies. In the 16 studies carried out among non-Asian populations, contrasting patterns were observed—that is, there was a statistically significantly increased risk for development of the intestinal type of gastric cancer in both homozygotes and carriers (ORHM = 1.49 ($I^2 = 56.2$) and ORCR = 1.42 ($I^2 = 51.9$)), and no specific associations were observed for the diffuse type of cancer.

IL1B-31 polymorphism

Thirty-two studies of the IL1B-31 polymorphism—with data from 17 studies in Asian populations (12, 21, 24, 25, 29, 31, 35, 37-41, 44-47) and 15 in non-Asian populations—ranged in Asian populations from 1.49 ($I^2 = 56.2$) and ORCR = 1.42 ($I^2 = 51.9$)), and no specific associations were observed for the diffuse type of cancer.
were considered (Web Table 6). The overall estimated odds ratios (ORHM and ORCR) for gastric cancer were 0.92 ($I^2 = 33.4$) and 0.94 ($I^2 = 41.2$), respectively. These odds ratios were not statistically significant. In studies from Asian populations, the corresponding odds ratios were 0.82 and 0.86, respectively, and were statistically significant. The odds ratios were further reduced and remained statistically significant when high-quality studies were considered (ORHM = 0.69 and ORCR = 0.74) and when analyses were restricted to $H. pylori$-positive subjects and controls (ORHM = 0.65 and ORCR = 0.76), with similar effects being seen in high-quality studies (ORHM = 0.53 and ORCR = 0.65). Corresponding odds ratios among all non-Asian population studies pointed in the opposite direction but were not statistically significant (ORHM = 1.09 and ORCR = 1.04).

### Table 2. Risk of Gastric Cancer Among Carriers of Polymorphisms in Inflammatory Response Genes, 1990–2006

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Direction of Association (No. of Studies)</th>
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<tbody>
<tr>
<td></td>
<td>Total</td>
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<tr>
<td></td>
<td>Asian Studies</td>
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<tr>
<td></td>
<td>Non-Asian Studies</td>
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</tbody>
</table>
| **IL1B-511T** | --- | — | —
| **IL1B-31C** | ↑$^b$ (17)$^{c,d}$ | ↓$^b$ (5)$^{c,d}$ | —
| **IL1B-3954T** | — | — | —
| **IL1RN2** | ↑$^b$ (39)$^{c,d}$ | ↑$^b$ (13)$^{c,d}$ | —
| **IL8-251A** | — | — | —
| **IL10-1082G** | ↑$^a$ (5) | — | —
| **IL10-819T** | — | — | —
| **IL10-592A** | ↓$^b$ (6)$^f$ | — | —
| **TNFA-308A** | — | — | —
| **TNFA-238A** | — | — | —

**Abbreviations:** IL, interleukin; TNF, tumor necrosis factor.

$^a$ Fewer than 5 studies.

$^b$ Decreased risk.

$^c$ This finding was also observed in $H. pylori$-positive subjects.

$^d$ This finding was also observed in homozygotes.

$^e$ Increased risk.

$^f$ $H. pylori$-positive subjects.

### Table 3. Risk of the Cardia Type of Gastric Cancer Among Carriers of Polymorphisms in Inflammatory Response Genes, 1990–2006

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Direction of Association (No. of Studies)</th>
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<tbody>
<tr>
<td></td>
<td>Total</td>
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<tr>
<td></td>
<td>Asian Studies</td>
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<tr>
<td></td>
<td>Non-Asian Studies</td>
</tr>
</tbody>
</table>
| **IL1B-511T** | — | — | —
| **IL1B-31C** | ↑$^b$ (8) | — | —
| **IL1B-3954T** | — | — | —
| **IL1RN2** | ↑$^b$ (10)$^{c,d}$ | ↑$^b$ (5)$^d$ | —
| **IL8-251A** | — | — | —
| **IL10-1082G** | — | — | —
| **IL10-819T** | — | — | —
| **IL10-592A** | — | — | —
| **TNFA-308A** | — | — | —
| **TNFA-238A** | — | — | —

**Abbreviations:** IL, interleukin; TNF, tumor necrosis factor.

$^a$ Fewer than 5 studies.

$^b$ Increased risk.

$^c$ This finding was also observed in $H. pylori$-positive subjects.

$^d$ This finding was also observed in homozygotes.
Anatomic site of gastric cancer. Overall, there was a statistically significant increased risk for 8 studies reporting results for the cardia subsite of gastric cancer (ORCR = 1.41), although the significance was not maintained in high-quality studies. In studies confined to non-Asian populations, the magnitude of the risk was increased (ORCR = 1.61), a result also observed within high-quality studies (ORCR = 1.68). An opposite trend was observed in studies conducted among Asian populations (ORHM = 0.81 and ORCR = 0.86), though this finding was not statistically significant. On the basis of 16 studies overall, ORHM and ORCR for the distal subsite of gastric cancer were 0.95 ($I^2 = 48.9$) and 1.02 ($I^2 = 60.5$),

Table 4. Risk of the Distal Type of Gastric Cancer Among Carriers of Polymorphisms in Inflammatory Response Genes, 1990–2006

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Direction of Association (No. of Studies)</th>
<th>Total</th>
<th>Asian Studies</th>
<th>Non-Asian Studies</th>
</tr>
</thead>
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<td>High-Quality Studies</td>
<td>All Studies</td>
<td>High-Quality Studies</td>
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<td>$IL1B-511T$</td>
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<td>$\uparrow^a (10)^b$</td>
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<td>$IL1B-31C$</td>
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<tr>
<td>$IL1RN2$</td>
<td>$\uparrow^a (25)^b,e$</td>
<td>$\uparrow^a (13)^b,e$</td>
<td>$-$</td>
<td>$-$</td>
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<tr>
<td>$IL8-251A$</td>
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<td>$-$</td>
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<td>$TNFA-238A$</td>
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</tbody>
</table>

Abbreviations: IL, interleukin; TNF, tumor necrosis factor.

- $^a$ Increased risk.
- $^b$ This finding was also observed in $H. pylori$-positive subjects.
- $^c$ Fewer than 5 studies.
- $^d$ Decreased risk.
- $^e$ $H. pylori$-positive subjects.
- $^f$ This finding was observed in homozygotes.

Table 5. Risk of the Intestinal Type of Gastric Cancer Among Carriers of Polymorphisms in Inflammatory Response Genes, 1990–2006

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Direction of Association (No. of Studies)</th>
<th>Total</th>
<th>Asian Studies</th>
<th>Non-Asian Studies</th>
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<td>All Studies</td>
<td>High-Quality Studies</td>
<td>All Studies</td>
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<td>$IL1B-511T$</td>
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<tr>
<td>$IL1RN2$</td>
<td>$\uparrow^d (25)^b,e$</td>
<td>$\uparrow^d (13)^b,e$</td>
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<td>$-$</td>
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<tr>
<td>$IL8-251A$</td>
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</table>

Abbreviations: IL, interleukin; TNF, tumor necrosis factor.

- $^a$ Decreased risk.
- $^b$ This finding was also observed in homozygotes.
- $^c$ Fewer than 5 studies.
- $^d$ Decreased risk.
- $^e$ This finding was also observed in $H. pylori$-positive subjects.

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respectively. These odds ratios were not statistically significant. In 6 Asian populations, the ORCR was 0.77; although this result was statistically significant, the significance was not maintained when only high-quality studies were considered (Web Table 6).

**Histologic type of gastric cancer.** No statistically significant effects were found for histologic type in studies overall. For 9 studies from Asian populations, the *IL1B*-31C allele was associated with a statistically significant reduced risk for the intestinal type of cancer (ORCR = 0.75) and for homozygotes (ORHM = 0.63).

**IL1B**-3954 *polymorphism*

Fourteen studies on the *IL1B*+3954 polymorphism, with data from 6 Asian (12, 19, 21, 22, 45) and 8 non-Asian (13, 50, 53, 54, 58, 64, 65) populations, were considered (Web Table 7). The overall estimated odds ratios (ORHM and ORCR) for gastric cancer for all studies combined were 0.96 ($I^2$ not significant) and 1.26 ($I^2 = 62.1$), on the basis of 7 and 14 studies, respectively. Results based specifically on studies carried out in non-Asian populations were very similar or identical to this. In studies from Asian populations, the ORCR among all studies was 1.63 ($I^2 = 74.5$). None of these odds ratios were statistically significant. In general, all results were similar in magnitude when analyses were restricted to *H. pylori*-positive cases and controls.

**IL1RN polymerorphism**

Thirty-nine studies on the *IL1RN* polymorphism, with data from 18 Asian populations (12, 18, 21–25, 28, 34, 37, 39–41, 44–46, 48) and 21 non-Asian populations (11, 13, 50–54, 56–60, 62–68, 70), were considered (Web Table 8). The overall estimated odds ratios (ORHM and ORCR) for gastric cancer were 1.39 ($I^2 = 62.7$) and 1.17 ($I^2 = 43.6$), respectively; results were statistically significant for carriers (Web Table 8). In the high-quality studies, the corresponding odds ratios were increased in magnitude (ORHM = 1.72 and ORCR = 1.32) and remained statistically significant. In high-quality studies from non-Asian populations, an increase in the magnitude of effect was found (ORHM = 1.84 ($I^2 = 53.5$) and ORCR = 1.47 ($I^2$ not significant), with the latter finding being statistically significant). In general, the results were also increased in magnitude when analyses were restricted to *H. pylori*-positive cases and controls (ORHM = 1.85 ($I^2 = 52.3$) and ORCR = 1.58 ($I^2$ not significant)). No statistically significant effects were found in studies from Asian populations.

**Anatomic site of gastric cancer.** Overall, there was a statistically significant effect for 10 studies reporting data on the cardia subsite (ORHM = 2.63 and ORCR = 1.34), and the association was maintained when analysis was restricted to high-quality studies (ORHM = 2.69), although this was not statistically significant for carriers (ORCR = 1.30). No statistically significant effect was found in studies from Asian populations. In studies from non-Asian populations, homozygotes for the 2 allele showed elevated risks (ORHM = 2.63), with similar results in high-quality studies (ORHM = 2.69). Based on 18 studies overall for the distal subsite of gastric cancer, ORHM and ORCR were 1.65 ($I^2 = 77.8$) and 1.29 ($I^2 = 45.2$), respectively; the latter finding was statistically significant, with similar results in high-quality studies. The results were increased in magnitude in the 6 studies carried out among Asian populations with *H. pylori*-positive cases and controls (ORCR = 1.57). The corresponding ORCR for *H. pylori*-positive cases and controls was 1.39 ($I^2 = 62.7$) and 1.17 ($I^2 = 43.6$), respectively; results were statistically significant for carriers (Table 8).
controls in high-quality studies of non-Asian populations was 1.53.

**Histologic type of gastric cancer.** In 25 studies restricted to the intestinal type of gastric cancer, the overall ORHM and ORCR were 1.83 ($I^2 = 57.2$) and 1.34 ($I^2 = 44.3$), respectively. The results were statistically significant. This effect was maintained in high-quality studies and was elevated in homozygotes (ORHM = 2.37). The same magnitude of effect was seen among studies from non-Asian populations (ORHM = 2.34 and ORCR = 1.60) but was not observed among studies from Asian populations. Overall, 26 studies had results for the diffuse type of gastric cancer; the ORHM was 1.72 ($I^2 = 46.1$) and was statistically significant, but the ORCR was 1.12 ($I^2 = 6.0$) and of borderline statistical significance. The magnitude of the effect was increased in high-quality studies (ORHM = 1.95) and was stronger still in *H. pylori*-positive cases and controls (ORHM = 2.45). The results in studies from non-Asian populations were very similar or identical.

### **IL8-251 polymorphism**

Twelve studies of the *IL8*-251 polymorphism considered results from 9 Asian (10, 18, 25, 26, 30, 36), and 3 non-Asian (49, 56, 61) populations (Web Table 9). The overall estimated odds ratios (ORHM and ORCR) for gastric cancer for all studies combined were 0.96 ($I^2 = 63.9$) and 1.04 ($I^2 = 60.8$), respectively. No results were statistically significant.

### **IL10-1082 polymorphism**

Ten studies of the *IL10*-1082 polymorphism with data from 5 Asian (20, 25, 27, 33, 39) and 5 non-Asian (49, 52, 63, 65, 70) populations were considered (Web Table 10). The overall estimated odds ratios (ORHM and ORCR) for gastric cancer for all studies combined were 1.40 ($I^2 = 73.0$) and 1.11 ($I^2 = 62.6$) on the basis of 9 and 10 studies, respectively. These results were not statistically significant. The result based specifically on studies from Asian populations showed a significantly increased risk in persons with G carrier status (ORCR = 1.57). Corresponding odds ratios among all studies from non-Asian populations were also statistically significant in the opposite direction (ORCR = 0.80). In general, all results were of the same magnitude when analysis was restricted to studies with *H. pylori*-positive cases and controls.

### **IL10-819 polymorphism**

Five studies considered results from 2 Asian (33, 39) and 3 non-Asian (49, 52, 65) populations (Web Table 11). The overall estimated odds ratios (ORHM and ORCR) for gastric cancer for all studies combined were 0.91 and 0.86. The results were not statistically significant.

### **IL10-592 polymorphism**

Eight studies on the *IL10*-592 polymorphism, with data from 3 Asian (20, 33, 39) and 5 non-Asian (49, 52, 63–65) populations, were considered (Web Table 12). The overall estimated odds ratios (ORHM and ORCR) for gastric cancer for all studies combined were 0.93 and 0.94, respectively. These results were not statistically significant.

### **TNFA-308 polymorphism**

Twenty-one studies of the *TNFA*-308 polymorphism, with data from 10 Asian (17, 20, 25, 28, 32, 35, 39, 43, 48, 71) and 11 non-Asian (11, 49, 52, 53, 56, 63, 66, 67, 69, 70) populations, were considered (Web Table 13). The overall estimated odds ratios (ORHM and ORCR) for gastric cancer for all studies combined were 1.23 and 1.09 on the basis of 14 and 21 studies, respectively. These results were not statistically significant.

### **Histologic type of gastric cancer.** A statistically significant increased risk for the diffuse type of cancer (ORCR = 1.33) was found among carriers, with a further increase in risk for studies with *H. pylori*-positive cases and controls (ORCR = 1.47).

### **TNFA-238 polymorphism**

Nine studies of the *TNFA*-238 polymorphism, with data from 6 Asian (25, 32, 35, 43, 71) and 3 non-Asian (49, 52, 53) populations, were considered (Web Table 14). The overall estimated odds ratios (ORHM and ORCR) for gastric cancer for all studies combined were 1.46 and 1.11 on the basis of 3 and 9 studies, respectively; these results were not statistically significant.

### **DISCUSSION**

Worldwide, the relation between polymorphisms in genes associated with inflammatory factors and the risk of gastric cancer has been investigated extensively since the landmark paper by El-Omar et al. (58) was published in 2000. Polymorphisms in several other genes related to inflammation have since been investigated in different populations in studies of variable quality. We conducted a series of meta-analyses, using a predefined protocol, in order to study the most frequently investigated genes, including those coding for interleukins (*IL1B, IL1RN, IL8*, and *IL10*) and *TNFA*. We included information about *IL1B*-3954T, *IL8*-251A, *IL10*-819T, and *TNFA*-238A carriers, but among these persons, we did not observe any statistically significant effects. The analyses presented revealed risk differences following stratification by histologic type, anatomic site, geographic location, and *H. pylori* infection status. We believe that the simultaneous consideration of meta-analyses for multiple polymorphisms within genes with related functions results in a broader overview and allows for more detailed comparisons of the evidence base. The assessment of all studies according to predefined quality criteria was another important strength of our approach.

In this review, the clearest results were found for the association with *IL1RN2*, where an increased risk of gastric cancer was observed. This appeared to be confined to non-Asian populations but was observed for both intestinal and diffuse cancers, as well as distal and, to a lesser extent, cardia cancers. Analyses restricted to high-quality studies...
or confined to *H. pylori*-positive cases and controls were supportive of the observed effect that was found in association with both carrier and homozygote status. The *IL1RN*22 genotype has been reported to cause high circulating IL-1α and IL-1β levels, possibly resulting in a severe and prolonged inflammatory response. We believe this is mirrored in our results and indicates the importance of *IL1RN* in the association with gastric cancer. Together with *IL1B*-31 and *IL1B*-511, *IL1RN* was the first polymorphism reported to be related to gastric cancer (58). *IL1B*-511 and *IL1B*-31 were reported to be in linkage disequilibrium early, a consequence being that subsequent studies investigated only 1 of these genes in order to save money and material. Linkage disequilibrium was observed for studies in which both SNPs were analyzed; however, because of the limitation of studies not reporting on both of the SNPs for all anatomic sites or all histologic types, the corresponding odds ratios do not always indicate absolute linkage disequilibrium.

In our meta-analysis, the clearest results relating to Asian populations were observed for *IL1B*-31, where C carrier status was associated with a reduced overall risk. This effect was also observed in analyses restricted to high-quality studies, and there is some evidence that the association is confined to cancer at distal subsites and of intestinal histology. The reduced risks may be explained by the high incidence of *H. pylori* infection in the Asian populations. The polymorphisms in genes related to IL-1β production might encourage a stronger reaction against the infection that further reduces the damage to the gastric cells and increases apoptosis of the epithelial cells, preventing the development of gastric cancer (72).

By contrast, in an association apparently confined to non-Asians, *IL1B*-511T carriers were found to have an increased risk of cardia gastric cancer specifically. This association was also observed in analyses restricted to high-quality studies but was less evident in association with distal cancers or in relation to any specific histologic subtype. Here, a stronger inflammatory reaction may instead increase the risk of cancer through damage to gastric cells and bacterial overgrowth and accumulation of toxic byproducts (72).

In a recently published meta-analysis by Kamangar et al. (6), no association was found between the *IL1B*-511, *IL1B*-31, and *IL1RN* polymorphisms and risk of developing gastric cancer independent of histologic type. These conclusions differ from our results, possibly because of fewer studies in the analysis and the lack of further stratification by study quality. On the other hand, Camargo et al. (5) and Wang et al. (7) suggested that *IL1B*-511T and *IL1RN*2 carriers had an increased risk of developing intestinal gastric cancer. Those studies (5, 7, 9), which also stratified the meta-analysis into Caucasian and Asian populations and included similar numbers of studies, showed results similar to ours.

Interestingly, the results for *IL10*-1082G showed entirely contrasting effects in Asians (increased risk) and non-Asians (decreased risk), although this contrast was not specifically confirmed within high-quality studies, possibly because of the low numbers of studies included. Recently, a meta-analysis confirmed the increase in Asian populations, but a limited number of Caucasian studies showed nonsignificant results (9). Finally, in carriers of *TNFA*-308A, there was good evidence for increased risk specific to diffuse cancers in non-Asians (supported by high-quality studies, but with no effect of *H. pylori* infection).

In recently published meta-analyses (4, 9), investigators reported an increased risk for gastric cancer in carriers of *TNFA*-308A among Caucasians, while increased risks for distal and intestinal cancers were also found in another meta-analysis (8), though with no further stratification by population.

There are some difficulties in the interpretation of our results. This systematic review and meta-analysis was built upon data collected from the current literature and through personal contact with authors when relevant results were not available from the publication. Not all of the authors contacted had access to data or could provide information for all polymorphisms, anatomic sites, or histologic types. As a result, some studies only contributed information to the overall gastric cancer analysis, whereas others contributed additionally to subanalyses (e.g., anatomic site-specific results). Therefore, the overall results cannot always be expected to reflect a weighted average result for the component anatomic locations. Few high-quality studies were conducted within Asian populations, and when we stratified by *H. pylori* infection status, some studies had to be excluded because of the lack of relevant information among controls. Differential misclassification of *H. pylori* infection could have occurred if, for example, the presence of gastric cancer results in atrophy, which can make detection less likely (73). Differences in our results as compared with earlier published meta-analyses may be due to the data collected from the included papers. Here we collected raw data based on information presented in the published articles or obtained from the contacted authors, and we recalculated the odds ratios and confidence intervals. Another problem resides in the fact that definitions (mainly concerning histologic type and site localization) may vary in different parts of the world (e.g., in Japan vs. the West), which can lead to inconsistency when study results are pooled together.

In conclusion, the importance of stratifying by gastric cancer type, site, *H. pylori* infection, geographic location, and study quality needs to be considered in future studies, together with consideration of associations with multiple genes with similar functions. The underlying genetic background of the population specifically must also be understood. Study quality considerations, both laboratory and epidemiologic, can also affect results and may help explain the variability in findings that have been published to date.

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