A Meta-Analysis of Interleukin-8 -251 Promoter Polymorphism Associated with Gastric Cancer Risk

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Abstract

Background: Potential functional allele A/T single nucleotide polymorphism (SNP) of Interleukin 8 (IL-8) promoter -251 has been implicated in gastric cancer risk.

Methods: We aimed to explore the role of A/T SNP of IL-8 -251 in the susceptibility to gastric cancer through a systematic review and meta-analysis. Each initially included article was scored for quality appraisal. Desirable data were extracted and registered into databases. Eighteen studies were ultimately eligible for the meta-analysis of IL-8 -251 A/T SNP. We adopted the most probably appropriate genetic model (codominant model). Potential sources of heterogeneity were sought out via stratification and sensitivity analyses, and publication biases were estimated.

Results: Between IL-8 -251 AA genotype with gastric cancer risk, statistically significant association could be noted with overall gastric cancer, evidently noted in Asians, witnessed in high quality subgroup, and apparently noted in intestinal-type gastric cancer.

Conclusions: Our meta-analysis indicates that IL-8 -251 AA genotype is associated with the overall risk of developing gastric cancer and may seem to be more susceptible to overall gastric cancer in Asian populations. IL-8 -251 AA genotype is more associated with the intestinal-type gastric cancer. IL-8 -251 AA genotype is not associated with Helicobacter Pylori infection status in our meta-analysis.

Impact: The analyses suggest that IL-8 -251 AA genotype may be an important biomarker of gastric cancer susceptibility for Asians, especially for Chinese Han population, the assumption that needs to be further confirmed in future well-designed studies in China.

Introduction

Nowadays, worldwide gastric cancer incidence has decreased but its mortality still ranks second [1]. In the midwestern rural areas of China [2], gastric cancer still constitutes one of the most lethal malignancies. As is widely known, infectious, dietary, environmental, and genetic factors are implicated in gastric carcinogenesis, but only a minority of persons exposed to risk factors such as Helicobacter pylori infection ultimately develop gastric cancer [3], which implies that host genetic susceptibility plays an important role in developing gastric cancer. Such various susceptibilities could be explained, in part, by single nucleotide polymorphisms (SNPs) of susceptible genes [4,5].

IL-8, one of key members of the human α-chemokine subfamily, acts as a potent chemoattractant and activator of neutrophils [6,7]. Highly expressed levels of IL-8 mRNA and protein were found in gastric cancer cells [8,9]. It has recently been suggested that IL-8 is closely related to the tumorigenesis, angiogenesis, adhesion, invasion or metastasis of cancer [10–14]. The IL-8 gene, located on chromosome 4q12-21, is 5.2 kb long and contains four exons and three introns. In the year 2000, Hull et al. reported a single A/T SNP at position -251 numbering from the transcription start site in the proximal promoter region and found that the IL-8 -251A allele tended to be associated with increased IL-8 production [15]. Thus, it could be extrapolated that IL-8 -251A allele may increase the risk of developing cancer through the elevation of its IL-8 expression.
In 2004, Savage et al. published the first study indicating that IL-8 -251A allele is associated with an increased risk for gastric cardia cancer [16]. Since then, researchers have consecutively reported associations of IL-8 -251A/T SNP with the susceptibility to gastric cancer, but with mixed or conflicting results [17–34]. Up to now, there have been five relevant published meta-analysis articles focusing on IL-8 -251A/T SNP [35–39], among which one [35] was published in Chinese. Two articles were dealt with the meta-analyses on overall cancer susceptibilities rather than gastric cancer susceptibility per se in details [38,39]. Unfortunately, those five meta-analyses all failed to adopt the most likely appropriate genetic model, and thus the authentic values of statistical results could be compromised.

Accordingly, the aim of our meta-analysis was to explore, using the most appropriate genetic model, the role of IL-8 -251 A/T SNP in the risk of developing gastric cancer and to identify possible sources of heterogeneity among the eligible studies.

Materials and Methods

Search Strategy

A systematic literature search was performed for articles regarding IL-8 -251 A/T SNP associated with the gastric cancer risk. The MEDLINE, EMBASE databases, Chinese National Knowledge Infrastructure (CNKI), Web of Science, and BIOSIS databases were used simultaneously with the combination of terms “Interleukin 8”, “IL-8”, “interleukin”, or “cytokine”, “gene”; “polymorphism”, “variant”, or “SNP”; and “gastric cancer”, “gastric carcinoma”, “diffuse gastric cancer” or “stomach cancer” from January 2000 to January 2011. The search was performed without any restriction on language. The scope of computerized literature search was expanded according to the reference lists of retrieved articles. The relevant original articles were also sought manually.

Study Selection

Studies concerning the association of IL-8 -251A/T SNP with the risk of developing gastric cancer were included if the following conditions were met: (i) any study described the association of IL-8 -251 A/T SNP with gastric cancer; (ii) any study reported the numbers of both controls and gastric cancer cases; (iii) results were expressed as odds ratio (OR) with 95% confidence intervals (CI); (ii) any study reported the odds ratios (OR) and 95% confidence intervals (95% CI) were used to assess the strength of associations between IL-8 -251 A/T SNP and gastric cancer risk. OR1, OR2, and OR3 regarding IL-8 -251 A/T SNP were calculated for genotypes AA versus TT, TA versus TT, and AA versus TA, respectively.

The above pairwise differences were used to determine the most appropriate genetic model. If OR1 = OR2 ≠ 1 and OR2 = 1, a recessive model is suggested. If OR1 = OR2 ≠ 1 and OR1 = 1, a dominant model is implied. If OR2 = 1/OR1 ≠ 1 and OR1 = 1, a complete overdominant model is suggested. If OR1 > OR2 > 1 and OR1 > OR2 > 1, or OR1 < OR2 < 1 and OR1 < OR2 < 1, a codominant model is indicated [43]. If a dominant model was indicated, the original grouping was collapsed and the new group of A carriers (AA plus TA) was compared with TT genotype; if a recessive model was suggested, AA was compared to the group of TT plus TA; if a complete overdominant model was implied, the group of AA plus TT was compared with TA; or if a codominant model was insinuated, AA was compared with TA and with TT, respectively.

The Q statistic was used to test for heterogeneity among the studies included in the meta-analysis. A fixed-effects model, using Mantel-Haenszel (M-H) method, was employed to calculate the pooled ORs when homogeneity existed on the basis of Q-test p value no less than 0.1. By contrast, a random-effects model, using DerSimonian and Laird method (D+S), was utilized if there was heterogeneity based on Q-test p value less than 0.1. The significance of pooled ORs was tested by Z test (P<0.05 was considered significant).

Sensitivity analysis was performed, in which the meta-analysis estimates were computed after every one study being omitted in each turn. Finally, publication bias was assessed by performing funnel plots qualitatively, and estimated by Begg’s and Egger’s tests quantitatively.

Results

Literature Search and Study Selection

After comprehensive searching, a total of 261 articles in English and 8 in Chinese were retrieved. In our meta-analysis were initially included altogether 19 studies [16–34] which catered to the inclusion criteria. Those 19 studies were preliminarily appropriate to the meta-analysis of the associations with gastric cancer regarding IL-8 -251A/T SNP. After careful reading of the full text of those studies, we found two studies investigated by seemingly different but actually almost the same authors [32,34], so we only included the study with larger sample size [34], that is, the study with smaller sample size [32] was finally excluded. The
| First author            | Year of publication | Quality assessment scores | Genotyping method | Total sample size | Number of controls | Number of cases | Study location | Ethnic group | P values for HWE | Controls, genotypes(n) | All Cases, genotypes(n) |
|-------------------------|---------------------|---------------------------|-------------------|-------------------|--------------------|----------------|----------------|--------------|----------------|-----------------------|------------------------|
| Savage SA et al.        | 2004                | 7                         | Multiplex         | 517               | 429                | 88             | China          | Asians       | 0.8848131    | 147 207 75 26 39 23     |                        |
| Lu W et al.             | 2005                | 6.5                       | DHPLC             | 550               | 300                | 250            | China          | Asians       | 0.5158484    | 119 144 37 94 102 54     |                        |
| Taguchi A et al.        | 2005                | 7                         | RFLP              | 648               | 252                | 396            | Japan          | Asians       | 0.9940137    | 125 105 22 161 191 44     |                        |
| Lee WP et al.           | 2005                | 6                         | RFLP              | 778               | 308                | 470            | Taiwan        | Asians       | 0.140368     | 108 138 62 198 213 59     |                        |
| Ohyampaedia M et al.    | 2005                | 7.5                       | Direct            | 456               | 244                | 212            | Japan          | Asians       | 0.8470500    | 149 84 11 93 106 13       |                        |
| Zeng ZR et al.          | 2005                | 6.5                       | RDB               | 402               | 196                | 206            | China          | Asians       | 0.0218768    | 43 114 39 37 110 59       |                        |
| Kamali-Sarvestani E et al. | 2006                | 5.75                      | ASO               | 172               | 153                | 19             | Iran           | Asians       | 0.7957565    | 57 74 22 4 6 9            |                        |
| Shirai K et al.         | 2006                | 5.5                       | RFLP              | 649               | 468                | 181            | Japan          | Asians       | 0.8304604    | 211 208 49 83 78 20       |                        |
| Savage SA et al.        | 2006                | 7.5                       | Taqman/MGB Eclipse | 715              | 428                | 287            | Poland         | Caucasians   | 0.3914650    | 106 205 117 71 140 76     |                        |
| Kamangar F et al.       | 2006                | 6                         | MGB Eclipse/Taqman | 319              | 207                | 112            | Finland        | Caucasians   | 0.0549341    | 72 111 24 42 56 14        |                        |
| Garza-Gonzalez E et al. | 2007                | 3.75                      | ARMS              | 285               | 207                | 78             | Mexico         | Hispanic     | 0.4918145    | 68 97 42 15 47 16         |                        |
| Crusius JB et al.       | 2008                | 8.5                       | Real-time PCR     | 1375              | 1139               | 236            | European       | Caucasians   | 0.7055677    | 315 574 250 75 113 48     |                        |
| Canedo P et al.         | 2008                | 6.5                       | Taqman            | 1026              | 693                | 333            | Portugal       | Caucasians   | 0.4979191    | 203 353 137 111 169 53     |                        |
| Ye BD et al.            | 2009                | 5.75                      | RFLP              | 359               | 206                | 153            | Korea          | Asians       | 0.5529341    | 97 86 23 54 82 17         |                        |
| Kang JM et al.          | 2009                | 7                         | RFLP              | 656               | 322                | 334            | Korea          | Asians       | 0.2256995    | 147 148 27 126 159 49     |                        |
| Ko KP et al.            | 2009                | 7                         | SNPs/Shot         | 389               | 308                | 81             | Korea          | Asians       | 0.1553548    | 135 146 27 34 35 12       |                        |
| Zhang L et al.          | 2010                | 8.5                       | RFLP              | 1023              | 504                | 519            | China          | Asians       | 0.7541397    | 160 251 93 130 261 128    |                        |
| Song B et al.           | 2010                | 5.5                       | RFLP              | 398               | 190                | 208            | China          | Asians       | 0.3894032    | 68 96 26 64 108 36        |                        |

*Data of cardia type of gastric cancer were accessible; Data of noncardia type of gastric cancer were accessible; Data of intestinal type of gastric cancer were accessible.
*Data of sporadic diffuse-type of gastric cancer were accessible; Data of intestinal-type of gastric cancer were accessible.
*Data of the status of Helicobacter pylori of gastric cancer were accessible.
Here participants, though treated as Asians geographically in this study, should be better considered as separate Iranian population conducted in our subgroup analysis due to its complex ethnic components.

Here participants in this study should be treated as Mexican or Hispanic population rather than Caucasian population [26,45].

RFLP: Restriction fragment length polymorphisms; DHPLC: PCR-based denaturing high-performance liquid chromatography; Taqman: TaqMan polymerase chain reaction method; SSCP: Single strand conformation polymorphism; Multiplex: Multiplex polymerase chain reaction method (a variant of PCR in which two or more loci are simultaneously amplified in the same reaction); Direct: Direct sequence analysis of polymerase chain reaction; RDB: polymerase chain reaction and reverse dot blot; ASO: oligonucleotide allele specific polymerase chain reaction; MGB Eclipse: MGB Eclipse Assay polymerase chain reaction method; ARMS: Amplification refractory mutation system polymerase chain reaction; SNPs/Shot: the SNPs/Shot assay which provides detection of certain SNPs.

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Figure 1. The flow chart of literature search and study selection.
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269 Articles identified
261 in English/ PubMed, etc.
8 in Chinese/ CNKI

239 Articles excluded (for title and abstract)
209 apparently unrelated to our meta-analysis
30 unrelated reviews

30 Articles considered for further evaluation

0 Additional studies identified from retrieved articles

30 Full-text articles considered for further evaluation

11 Article excluded
1 related to the risk of atrophic gastritis and intestinal metaplasia
3 related to meta-analysis
2 related to cachexia
2 related to angiogenesis
1 related to H. pylori cagA gene and IL-8 production
1 related to mitochondrial DNA instability and IL-8 level
1 related to different strains of H. pylori and IL-8 level

19 studies initially included
18 in English
1 in Chinese

1 Article in English excluded
We excluded 1 study with smaller sample size investigated by the same authors who conducted the research with larger sample size

18 studies ultimately included
17 in English
1 in Chinese
### PART A

| Study ID | OR (95% CI) | % | Weight |
|----------|-------------|---|--------|
| Asians   |             |   |        |
| Savage SA et al. (2004) | 1.73 (0.93, 3.24) | 5.37 |
| Lu W et al. (2005) | 1.89 (1.12, 3.04) | 6.29 |
| Taguchi A et al. (2005) | 1.55 (0.88, 2.73) | 5.82 |
| Lee WP et al. (2005) | 0.52 (0.34, 0.80) | 6.84 |
| Ohyakuh M et al. (2005) | 1.89 (0.81, 4.40) | 4.04 |
| Zeng ZR et al. (2005) | 1.76 (0.97, 3.19) | 5.57 |
| Kamnani-Sarvestani E et al. (2006) | 5.83 (1.63, 20.89) | 2.37 |
| Shirai K et al. (2006) | 1.04 (0.58, 1.85) | 5.70 |
| Ye BD et al. (2009) | 1.33 (0.65, 2.70) | 4.82 |
| Kang JM et al. (2009) | 2.12 (1.25, 3.58) | 6.08 |
| Ko KP et al. (2009) | 1.76 (0.81, 3.84) | 4.41 |
| Zhang L et al. (2010) | 1.69 (1.19, 2.41) | 7.39 |
| Song B et al. (2010) | 1.47 (0.80, 2.71) | 5.49 |
| Subtotal (I² = 63.9%, p = 0.001) | 1.52 (1.16, 2.00) | 70.17 |

Caucasians

| Study ID | OR (95% CI) | % | Weight |
|----------|-------------|---|--------|
| Savage SA et al. (2006) | 0.87 (0.64, 1.17) | 6.91 |
| Kamnani-F et al. (2006) | 1.00 (0.47, 2.14) | 4.50 |
| Crusius JBJ et al. (2008) | 0.61 (0.41, 0.94) | 7.05 |
| Caneco P et al. (2008) | 0.71 (0.48, 1.05) | 7.09 |
| Subtotal (I² = 0.0%, p = 0.700) | 0.83 (0.66, 1.04) | 25.56 |

Hispanic

| Study ID | OR (95% CI) | % | Weight |
|----------|-------------|---|--------|
| Garza-Gonzalez E et al. (2007) | 1.73 (0.77, 3.85) | 4.27 |
| Subtotal (I² = 0.0%, p = 0.700) | 1.73 (0.77, 3.85) | 4.27 |

Overall (I² = 66.7%, p = 0.000) | 1.32 (1.05, 1.66) | 100.00 |

NOTE: Weights are from random effects analysis

### PART B

| Study ID | OR (95% CI) | % | Weight |
|----------|-------------|---|--------|
| Asians   |             |   |        |
| Savage SA et al. (2004) | 1.73 (0.93, 3.24) | 5.37 |
| Lu W et al. (2005) | 1.89 (1.12, 3.04) | 6.29 |
| Taguchi A et al. (2005) | 1.55 (0.88, 2.73) | 5.82 |
| Lee WP et al. (2005) | 0.52 (0.34, 0.80) | 6.84 |
| Ohyakuh M et al. (2005) | 1.89 (0.81, 4.40) | 4.04 |
| Zeng ZR et al. (2005) | 1.76 (0.97, 3.19) | 5.57 |
| Kamnani-Sarvestani E et al. (2006) | 5.83 (1.63, 20.89) | 2.37 |
| Shirai K et al. (2006) | 1.04 (0.58, 1.85) | 5.70 |
| Ye BD et al. (2009) | 1.33 (0.65, 2.70) | 4.82 |
| Kang JM et al. (2009) | 2.12 (1.25, 3.58) | 6.08 |
| Ko KP et al. (2009) | 1.76 (0.81, 3.84) | 4.41 |
| Zhang L et al. (2010) | 1.69 (1.19, 2.41) | 7.39 |
| Song B et al. (2010) | 1.47 (0.80, 2.71) | 5.49 |
| Subtotal (I² = 63.9%, p = 0.001) | 1.52 (1.16, 2.00) | 70.17 |

Caucasians

| Study ID | OR (95% CI) | % | Weight |
|----------|-------------|---|--------|
| Savage SA et al. (2006) | 0.97 (0.64, 1.47) | 6.91 |
| Kamnani-F et al. (2006) | 1.00 (0.47, 2.14) | 4.50 |
| Crusius JBJ et al. (2008) | 0.61 (0.41, 0.94) | 7.05 |
| Caneco P et al. (2008) | 0.71 (0.48, 1.05) | 7.09 |
| Subtotal (I² = 0.0%, p = 0.700) | 0.83 (0.66, 1.04) | 25.56 |

Hispanic

| Study ID | OR (95% CI) | % | Weight |
|----------|-------------|---|--------|
| Garza-Gonzalez E et al. (2007) | 1.73 (0.77, 3.85) | 4.27 |
| Subtotal (I² = 0.0%, p = 0.700) | 1.73 (0.77, 3.85) | 4.27 |

Overall (I² = 66.7%, p = 0.000) | 1.32 (1.05, 1.66) | 100.00 |

NOTE: Weights are from random effects analysis
surnames and names of the authors [34] were rectified, that is, Bo S. et al were changed into Song B. et al for correct citation.

Traditionally speaking, any study that deviated from HWE should have been removed; however, Minelli C et al, recently pointed out that studies that appear to deviate from HWE should be investigated further rather than just excluded unless there are other grounds for doubting the quality of the study [34]. To date, it is still inconclusive whether studies deviated from HWE should be included or excluded in conducting meta-analysis. In our meta-analysis, one study [21] was deviated from HWE; however, considering that the number of participants in this study was large and given that sensitivity analyses would be conducted, we finally remained this study in our meta-analysis.

Thus, 18 studies [16–31,33,34] with a total of 6554 controls and 4163 cases were ultimately eligible for the meta-analysis of IL-8 -251 A/T SNP. The corresponding characteristics were seen in Table 1. The flow chart of literature search and study selection was illustrated in Figure 1.

Overall Meta-analysis and Subgroup Analyses

\( \text{OR}_1 (p \text{ value}), \text{OR}_2 (p \text{ value}), \text{and OR}_3 (p \text{ value}) \) of IL-8 -251 A/T SNP were 1.32 (p = 0.018), 1.12 (p = 0.082), and 1.17 (p = 0.092), respectively, possibly insinuating a codominant model effect of putative susceptible A allele (\( \text{OR}_1 > \text{OR}_2 > 1 \) and \( \text{OR}_1 > \text{OR}_3 > 1 \)). To further determine whether the adoption of codominant genetic model is influenced by the study deviated from HWE [21], the recalculated \( \text{OR}_1 \) (p value), \( \text{OR}_2 \) (p value), and \( \text{OR}_3 \) (p value) of IL-8 -251 A/T SNP, after the study [21] had been removed, became 1.30 (p = 0.032), 1.13 (p = 0.094), and 1.15 (p = 0.155), respectively, also possibly insinuating a codominant model effect of putative susceptible A allele. Considering that the participants in the study [21] were Asians, we calculated \( \text{OR}_1 \) (p value), \( \text{OR}_2 \) (p value), and \( \text{OR}_3 \) (p value) of IL-8 -251 A/T SNP among Asian participants, with both the inclusion and the exclusion of the study [21], and their values became 1.52 (1.16–2.00, p = 0.003), 1.19 (1.02–1.38, p = 0.023), and 1.31 (1.04–1.66, p = 0.024) when the study [21] was included and 1.51 (1.12–2.02, p = 0.006), 1.19 (1.02–1.39, p = 0.029), and 1.29 (1.00–1.67, p = 0.050) when the study [21] was excluded, definitely indicating a codominant model effect of putative susceptible A allele among Asians (\( \text{OR}_1 > \text{OR}_2 > 1 \) and \( \text{OR}_1 > \text{OR}_3 > 1 \)) with almost all their p values statistically significantly less than 0.05 or one just reached 0.05. Thus, the inclusion of the study with deviation from HWE [21] does not influence the adoption of the most probable genetic model (codominant model) in our meta-analysis. The genotype AA was compared with the genotype TA (AA vs TA) and with the genotype TT (AA vs TT), respectively. In Figure 2, for overall gastric cancer no statistically significant finding could be observed (AA vs TA), whereas a statistically significant finding could be noted (AA vs TT) from the facts that the pooled OR (95% CI, p value) was 1.17 (0.98–1.40, p = 0.092) for the former but 1.32 (1.05–1.66, p = 0.018) for the latter. The data were stratified, in the light of the ethnicity of participants, into Caucasians, Asians, and Hispanic. Also in Figure 2, the apparently opposite tendency could be noted between Caucasians and Asians, and statistically significant findings were noted in Asians but not in Caucasians (AA vs TT). The pooled ORs (95% CIs, p value) were 1.52 (1.16–2.00, p = 0.003) and 0.85 (0.66–1.04, p = 0.100) in Asians and Caucasians (AA vs TT) or 1.31 (1.04–1.66, p = 0.024) and 0.93 (0.76–1.13, p = 0.453) in Asians and Caucasians (AA vs TA), respectively. Although the pooled OR could not be appraised in Hispanic participants, among which only one study was conducted in that ethnicity [26], the ethnicity that should be treated as Mexican or Hispanic rather than Caucasian [26,45], the individual OR was still apparent, being 1.73 (0.77–3.55, p = 0.182) and 0.79 (0.40–1.54, p = 0.484) in Figure 2. We further sub-stratified Asians into the participants from China, Taiwan China, Japan, Korea and Iran. As in Figure 3, the apparently discrepant tendency could be noted in the study from Taiwan China [19], the individual OR (95% CIs, p value) of which was 0.52 (0.34–0.80, p = 0.003); whereas the similar tendency could be noted in the studies from China, Japan, and Korea, the ORs (95% CIs, p value) of which were 1.71 (1.36–2.13, p = 0.000), 1.37 (0.95–1.98, p = 0.087), and 1.79 (1.23–2.59, p = 0.002), thus indicating statistically significant findings of increased risk for participants in China or Korea (AA vs TT). Likewise, similar findings were observed in the mode (AA vs TA) with 1.50 (1.22–1.83, p = 0.000), 1.06 (0.74–1.53, p = 0.743), 1.36 (0.81–2.29, p = 0.246), and 0.62 (0.41–0.93, p = 0.023) in China, Japan, Korea, and Taiwan China, respectively. Also interestingly, statistically significant finding was even more apparently noted in Iran because the individual OR for Iran (95% CIs, p value) was 5.83 (1.63–20.89, p = 0.007) and 5.05 (1.62–15.73, p = 0.005) in the mode (AA vs TT) and mode (AA vs TA), respectively.

As shown in Table 2 and Table 3, specific data for IL-8 -251 A/T SNP were stratified, on the basis of sample size, into two subgroups: small sample (the total number of controls and cases not less than 500) and small-and-moderate sample (the total number of controls and cases less than 500) subgroups. Statistically significant finding was noted in small-and-moderate sample subgroup but not in large sample counterpart (AA vs TT), given that the pooled ORs (95% CIs, p value) were 1.62 (1.25–2.10, p = 0.000) for the former and 1.16 (0.86–1.57, p = 0.340) for the latter, respectively.

The data were also stratified, in accordance with the quality appraisal scores, into high quality (scores no less than 6.5) and low-and-moderate quality (scores less than 6.5) subgroups. A statistically significant finding was witnessed in high quality subgroup but not in low-and-moderate quality counterpart, given that the pooled ORs (95% CIs, p value) were 1.38 (1.07–1.78, p = 0.013) for the former and 1.23 (0.77–1.97, p = 0.388) for the latter (AA vs TT), and 1.25 (1.03–1.51, p = 0.023) for the former and 1.03 (0.71–1.49, p = 0.892) for the latter (AA vs TA), respectively.

The data were additionally stratified, in line with publication time, into the earlier publication subgroup (articles published before or in 2005) and the later publication subgroup (articles published after 2005). No statistically significant findings were observed on the grounds that the pooled ORs (95% CIs, p value) were 1.39 (0.83–2.28, p = 0.191) in the former and 1.28 (0.99–1.66, p = 0.063) in the latter (AA vs TT), and 1.23 (0.62–1.85, p = 0.326) in the former and 1.13 (0.93–1.37, p = 0.222) in the latter (AA vs TA), respectively.

When gastric cancer was classified into non-cardia (or distal) and cardia subtypes, no statistically significant findings were found among non-cardia type or among cardia type on the grounds that
### Table A

| Study ID | OR (95% CI) | Weight |
|----------|-------------|---------|
| China    |             |         |
| Seave SA et al. (2004) | 1.73 (0.93, 3.24) | 7.64 |
| Lu W et al. (2005) | 1.86 (1.12, 3.04) | 8.98 |
| Zeng ZR et al. (2005) | 1.76 (0.97, 3.19) | 7.93 |
| Zhang L et al. (2010) | 1.69 (1.19, 2.41) | 10.58 |
| Song B et al. (2010) | 1.47 (0.80, 2.71) | 7.81 |
| Subtotal (I-squared = 0.0%, p = 0.987) | 1.71 (1.36, 2.13) | 42.92 |
| Japan    |             |         |
| Taguchi A et al. (2005) | 1.55 (0.88, 2.73) | 8.29 |
| Ohyuuchi M et al. (2005) | 1.89 (0.81, 4.40) | 5.76 |
| Shira K et al. (2006) | 1.04 (0.58, 1.85) | 8.12 |
| Subtotal (I-squared = 0.0%, p = 0.440) | 1.37 (0.95, 1.96) | 22.16 |
| Taiwan China |           |         |
| Lee WP et al. (2005) | 0.52 (0.34, 0.80) | 9.76 |
| Subtotal (I-squared = 0%, p = .) | 0.52 (0.34, 0.80) | 9.76 |
| Korea    |             |         |
| Ye BD et al. (2009) | 1.33 (0.65, 2.70) | 6.85 |
| Kang JM et al. (2009) | 2.12 (1.25, 3.58) | 8.67 |
| Ko KP et al. (2009) | 1.76 (0.81, 3.44) | 6.27 |
| Subtotal (I-squared = 0.0%, p = 0.585) | 1.79 (1.23, 2.59) | 21.80 |
| Overall (I-squared = 63.9%, p = 0.001) | 1.52 (1.16, 2.00) | 100.00 |

**NOTE:** Weights are from random effects analysis

### Table B

| Study ID | OR (95% CI) | Weight |
|----------|-------------|---------|
| China    |             |         |
| Seave SA et al. (2004) | 1.63 (0.91, 2.90) | 7.78 |
| Lu W et al. (2005) | 2.06 (1.26, 3.36) | 8.98 |
| Zeng ZR et al. (2005) | 1.97 (0.97, 3.34) | 9.06 |
| Zhang L et al. (2010) | 1.32 (0.96, 1.82) | 11.55 |
| Song B et al. (2010) | 1.23 (0.69, 2.19) | 7.83 |
| Subtotal (I-squared = 0.0%, p = 0.586) | 1.50 (1.22, 1.83) | 45.22 |
| Japan    |             |         |
| Taguchi A et al. (2005) | 1.10 (0.63, 1.93) | 7.96 |
| Ohyuuchi M et al. (2005) | 0.94 (0.40, 2.20) | 5.03 |
| Shira K et al. (2006) | 1.09 (0.51, 1.95) | 7.74 |
| Subtotal (I-squared = 0.0%, p = 0.949) | 1.06 (0.74, 1.53) | 20.73 |
| Taiwan China |           |         |
| Lee WP et al. (2005) | 0.62 (0.41, 0.93) | 10.06 |
| Subtotal (I-squared = 0%, p = .) | 0.62 (0.41, 0.93) | 10.06 |
| Korea    |             |         |
| Ye BD et al. (2009) | 0.78 (0.39, 1.55) | 6.43 |
| Kang JM et al. (2009) | 1.69 (1.00, 2.84) | 8.55 |
| Ko KP et al. (2009) | 1.86 (0.86, 4.02) | 6.68 |
| Subtotal (I-squared = 47.0%, p = 0.151) | 1.36 (0.81, 2.29) | 20.66 |
| Overall (I-squared = 56.4%, p = 0.005) | 1.31 (1.04, 1.66) | 100.00 |

**NOTE:** Weights are from random effects analysis
the pooled ORs (95% CIs, p value) were 1.05 (0.73–1.51, p = 0.783) among non-cardia type and 1.20 (0.72–2.00, p = 0.481) among cardia type (AA vs TT), and 0.85 (0.70–1.04 p = 0.122) among non-cardia type and 1.22 (0.97–1.53, p = 0.092) among cardia type (AA vs TA).

In terms of H. pylori infection status, no statistically significant findings were found among H. pylori negative controls (compared with H. pylori positive controls), for pooled ORs (95% CIs, p value) were 1.56 (0.76–3.21, p = 0.230) in the former and 0.99 (0.59–1.63, p = 0.967) in the latter (AA vs TT), and 1.22 (0.62–2.43, p = 0.564) in the former and 0.88 (0.57–1.38, p = 0.589) in the latter (AA vs TA), as shown in Figure 4.

And when genotyping techniques were considered, a statistically significant finding was noted in other genotyping technique subgroup but not in traditional PCR-RFLP subgroup (AA vs TT). In the PCR-RFLP subgroup and in other genotyping technique subgroup, pooled ORs (95% CIs, p value) were 1.28 (0.86–1.89, p = 0.223) in the former and 1.34 (1.00–1.80, p = 0.048) in the latter (AA vs TT).

Sensitivity Analysis

Meta-analyses were conducted repeatedly when each particular study had been removed. The results indicated that fixed-effects estimates and/or random-effects estimates before and after the deletion of each study were similar at large, suggesting high stability of the meta-analysis results. As shown in Figure 5, the most influencing single study on the overall pooled estimates seemed to be the study conducted by Lee WP et al. [19], the sensitivity analysis, however, indicated high stability of the results from the facts that the ORs (95% CI, p value) were 1.32 (1.05–1.66, p = 0.018) before the removal of that study and 1.39 (1.13–1.70, p = 0.002) after the removal of that study (AA vs TT).

Cumulative Meta-analysis

Cumulative meta-analyses of IL-8 -251 A/T SNP association were also conducted among Asians via the assortment of both total number of sample size (Figure 6 part A) and publication time (Figure 6 part B). As shown in Figure 6 part A, the inclinations, though undulated, toward significant associations could be seen when sorted by total sample size among Asians (AA vs TT). In Figure 6 part B was shown the cumulative meta-analysis of

### Table 2. Stratification for the test of heterogeneity on IL-8 -251 AA vs TA based on a codominant model.

| Q-test | OR(95% CI) | P value |
|--------|------------|---------|
| chi-squared | d.f. | p |
| Overall | 35.96 | 17 | 0.005 | 1.17(0.98–1.40) | 0.092 |
| Large sample | 23.18 | 9 | 0.006 | 1.12 (0.90–1.40) | 0.305 |
| Small-and-moderate sample | 11.75 | 7 | 0.109 | 1.25 (0.98–1.59) | 0.067 |
| High quality | 17.88 | 10 | 0.057 | 1.25 (1.03–1.51) | 0.023 |
| Low-and-moderate quality | 14.28 | 6 | 0.027 | 1.03 (0.71–1.49) | 0.892 |
| Publication before or in 2005 | 17.20 | 5 | 0.004 | 1.23(0.82–1.85) | 0.326 |
| Publication after 2005 | 18.40 | 11 | 0.000 | 1.32 (1.05–1.66) | 0.018 |
| Caucasians | 0.98 | 3 | 0.806 | 0.93 (0.76–1.13) | 0.453 |
| Asians | 27.54 | 12 | 0.006 | 1.31 (1.04–1.66) | 0.024 |
| Non-cardia type | 4.56 | 7 | 0.714 | 0.85 (0.70–1.04) | 0.122 |
| Cardia type | 4.77 | 4 | 0.311 | 1.22 (0.97–1.55) | 0.092 |
| Intestinal type | 4.96 | 6 | 0.549 | 1.08 (0.83–1.40) | 0.583 |
| Diffuse type | 6.42 | 3 | 0.093 | 0.89 (0.52–1.53) | 0.672 |
| Hp positive | 14.11 | 3 | 0.003 | 1.22 (0.62–2.43) | 0.564 |
| Hp negative | 2.43 | 2 | 0.297 | 0.88 (0.57–1.38) | 0.589 |
| PCR-RFLP genotyping | 12.46 | 6 | 0.052 | 1.07 (0.82–1.41) | 0.607 |
| Other genotyping | 23.23 | 10 | 0.010 | 1.25 (0.97–1.61) | 0.084 |

* M-H ORs (95% CI), otherwise D+L ORs (95% CI).

### Table 3. Stratification for the test of heterogeneity on IL-8 -251 AA vs TA based on a codominant model.

| Q-test | OR(95% CI) | P value |
|--------|------------|---------|
| chi-squared | d.f. | p |
| Overall | 51.03 | 17 | 0.000 | 1.32 (1.05–1.66) | 0.018 |
| Large sample | 38.78 | 9 | 0.000 | 1.16 (0.86–1.57) | 0.340 |
| Small-and-moderate sample | 6.08 | 7 | 0.530 | 1.62 (1.25–2.10) | 0.000 |
| High quality | 27.54 | 10 | 0.002 | 1.38 (1.07–1.78) | 0.013 |
| Low-and-moderate quality | 23.26 | 6 | 0.002 | 1.23 (0.77–1.97) | 0.388 |
| Publication before or in 2005 | 22.46 | 5 | 0.000 | 1.39(0.85–2.28) | 0.191 |
| Publication after 2005 | 28.50 | 11 | 0.003 | 1.28 (0.99–1.66) | 0.063 |
| Caucasians | 1.42 | 3 | 0.700 | 0.83 (0.66–1.04) | 0.100 |
| Asians | 33.20 | 12 | 0.001 | 1.52 (1.16–2.00) | 0.003 |
| Non-cardia type | 19.22 | 7 | 0.008 | 1.05 (0.73–1.51) | 0.783 |
| Cardia type | 12.12 | 4 | 0.016 | 1.20 (0.72–2.00) | 0.481 |
| Intestinal type | 7.00 | 6 | 0.321 | 1.37 (1.05–1.79) | 0.021 |
| Diffuse type | 12.14 | 3 | 0.007 | 1.24 (0.57–2.70) | 0.595 |
| Hp positive | 22.19 | 4 | 0.000 | 1.56 (0.76–3.21) | 0.230 |
| Hp negative | 4.88 | 3 | 0.181 | 0.99 (0.59–1.65) | 0.967 |
| PCR-RFLP genotyping | 24.26 | 6 | 0.000 | 1.28 (0.86–1.89) | 0.223 |
| Other genotyping | 26.45 | 10 | 0.003 | 1.34 (1.00–1.80) | 0.048 |

* M-H ORs (95% CI), otherwise D+L ORs (95% CI).

P values of M-H estimates, otherwise P values of D+L estimates.

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### PART A

| Study ID | OR (95% CI) | Weight |
|----------|-------------|--------|
| Lee WP et al. (2005) | 0.58 (0.28, 1.15) | 11.93 |
| Zeng ZR et al. (2005) | 1.48 (0.58, 3.80) | 9.87 |
| Kang JM et al. (2009) | 3.30 (0.60, 18.26) | 5.30 |
| Zhang L et al. (2010) | 0.95 (0.59, 1.55) | 13.63 |
| Subtotal ($\chi^2$-squared = 38.5%, $p = 0.181$) | 0.99 (0.59, 1.65) | 40.72 |

### PART B

| Study ID | OR (95% CI) | Weight |
|----------|-------------|--------|
| Lee WP et al. (2005) | 0.40 (0.20, 0.77) | 12.16 |
| Ohyauchi M et al. (2005) | 1.89 (0.81, 4.40) | 10.66 |
| Zeng ZR et al. (2005) | 1.98 (0.88, 4.46) | 10.90 |
| Kang JM et al. (2009) | 2.03 (1.16, 3.54) | 13.06 |
| Zhang L et al. (2010) | 3.07 (1.64, 5.72) | 12.51 |
| Subtotal ($\chi^2$-squared = 82.0%, $p = 0.000$) | 1.56 (0.76, 3.21) | 59.28 |
| Overall ($\chi^2$-squared = 74.9%, $p = 0.000$) | 1.34 (0.83, 2.17) | 100.00 |

**NOTE:** Weights are from random effects analysis.
association for IL-8 -251 A/T SNP with overall gastric cancer among Asians in chronological order (AA vs TT).

Publication Bias Analysis

Publication bias was preliminarily examined by funnel plots qualitatively and estimated by Begg’s and Egger’s tests quantitatively. Its funnel plot (Figure 7) showed that dots nearly symmetrically distributed, predominantly within pseudo 95% confidence limits (AA vs TA). P values were 0.198 (AA vs TT) and 0.495 (AA vs TA) in Begg’s test, insinuating no publication bias but p values were 0.031 (AA vs TT), insinuating a little publication bias but 0.171 (AA vs TA) in Egger’s test, insinuating no publication bias.

Discussion

In our meta-analysis, a statistically significant finding could be noted (AA vs TT) with the overall risk of developing gastric cancer; the apparently opposite tendency could be noted between Caucasians and Asians, and statistically significant findings were even more apparently noted in Asians, especially in Chinese Han population, but not in Caucasians (AA vs TT). Our meta-analyses suggest that IL-8 -251 AA genotype may be an important biomarker of gastric cancer susceptibility for Asians, especially for Chinese Han population, the assumption that needs to be further confirmed in future well-designed studies in China.

Based on the findings of cumulative meta-analyses, the inclinations, though undulated, toward significant associations in Asians could be obviously seen when sorted by total sample size (AA vs TT). The IL-8 -251 AA genotype may seem to be more susceptible to gastric cancer in Asians. Thus, the different or even conflicting risk associations, if so, among different ethnicities should be further meticulously investigated and reconfirmed in the future.

Our subgroup analyses also indicate that significant associations could be found in the small-and-moderate sample subgroup but not in the large sample counterpart (AA vs TT). In large sample subgroup the influences of ORs in the studies conducted by Lee et al. [19] and Kang et al. [30] are both oppositely strong enough (0.52 and 2.12, respectively) to offset the overall OR, thus the insignificant value (1.16) could be reached, whereas in small-and-moderate sample subgroup the ORs are averagely distributed around 1, but the influence of OR in the study conducted by Kamali-Sarvestani et al. [22] is strong enough (5.83) to make the overall OR to reach the significant value (1.62). A statistically significant finding was also witnessed in high quality subgroup but not in low-and-moderate quality counterpart (AA vs TT or AA vs TA). It is natural that high-quality studies should be designed in the future so as to accurately explore the real associations between IL-8 -251 A/T SNP and gastric cancer.

Additionally, 8 [18–20,23–25,27,29] out of 18 eligible studies were dealt with noncardia gastric cancer and 5 [16,18,19,27,33] with cardia gastric cancer. No statistically significant findings could be noted with either subgroup. 7 studies [18–20,25,26,29,30] in our meta-analysis were dealt with pathologically intestinal-type gastric cancer and 4 [18,19,26,30] out of 18 studies were dealt with pathologically diffuse-type gastric cancer. A statistically significant finding could be noted in intestinal-type but not in

![Figure 4. Odds ratios (ORs) for associations between IL-8 -251 A/T SNP and gastric cancer risk with different H pylori infection status. H pylori infection status includes H pylori positive cases versus positive controls and H pylori negative cases versus negative controls. The sizes of the squares indicate the relative weight of each study. Bars, 95% confidence interval (CI). A) The IL-8 -251 AA genotype versus TT genotype; B) The IL-8 -251 AA genotype versus TA genotype. doi:10.1371/journal.pone.0028083.g004](image)

![Figure 5. Influence analysis of the summary odds ratio coefficients on the association for the IL-8 -251 AA genotype with gastric cancer risk. Results were computed by omitting each study (on the left) in turn. Bars, 95% confidence interval. Meta-analysis random-effects estimates (exponential form) were used. doi:10.1371/journal.pone.0028083.g005](image)
### PART A

| Study                  | Year | Odds Ratio (95% CI) |
|------------------------|------|--------------------|
| Kamali-Sarvestani E et al. | 2006 | 5.83 (1.63, 20.89) |
| Ye BD et al.           | 2009 | 1.88 (1.01, 3.50)  |
| Ko KP et al.           | 2009 | 1.84 (1.13, 2.98)  |
| Song B et al.          | 2010 | 1.68 (1.15, 2.46)  |
| Zeng ZR et al.         | 2005 | 1.71 (1.24, 2.35)  |
| Ohyauchi M et al.      | 2005 | 1.73 (1.28, 2.33)  |
| Savage SA et al.       | 2004 | 1.73 (1.32, 2.27)  |
| Lu W et al.            | 2005 | 1.76 (1.38, 2.23)  |
| Taguchi A et al.       | 2005 | 1.72 (1.38, 2.14)  |
| Shirai K et al.        | 2006 | 1.82 (1.32, 2.18)  |
| Kang JM et al.         | 2009 | 1.68 (1.38, 2.03)  |
| Lee WP et al.          | 2005 | 1.38 (1.16, 1.64)  |
| Zhang L et al.         | 2010 | 1.44 (1.23, 1.68)  |

### PART B

| Study                  | Year | Odds Ratio (95% CI) |
|------------------------|------|--------------------|
| Savage SA et al.       | 2004 | 1.73 (0.93, 3.24)  |
| Zeng ZR et al.         | 2005 | 1.75 (1.13, 2.69)  |
| Ohyauchi M et al.      | 2005 | 1.78 (1.21, 2.61)  |
| Lu W et al.            | 2005 | 1.80 (1.33, 2.44)  |
| Taguchi A et al.       | 2005 | 1.74 (1.33, 2.28)  |
| Lee WP et al.          | 2005 | 1.24 (0.99, 1.55)  |
| Kamali-Sarvestani E et al. | 2006 | 1.30 (1.04, 1.62)  |
| Shirai K et al.        | 2006 | 1.26 (1.02, 1.55)  |
| Ye BD et al.           | 2009 | 1.27 (1.04, 1.55)  |
| Ko KP et al.           | 2009 | 1.26 (1.06, 1.57)  |
| Kang JM et al.         | 2009 | 1.37 (1.14, 1.64)  |
| Song B et al.          | 2010 | 1.38 (1.16, 1.64)  |
| Zhang L et al.         | 2010 | 1.44 (1.23, 1.68)  |
diffuse-type cancer (AA vs TT). As is known, cardia-type gastric cancer differs from noncardia-type gastric cancer in etiology, pathology, carcinogenesis, and/or prognosis [46–48], so is intestinal-type cancer versus diffuse-type cancer. It could be said that the indiscriminate combination of cardia-type and noncardia-type cases or intestinal-type and diffuse-type cases in the majority of eligible studies may mask or at least underestimate the real strength of the associations [5,42].

Furthermore, *Helicobacter pylori* infection is associated with increased epithelial IL-8 expression and mucosal secretion of IL-8 and *Helicobacter pylori* induced IL-8 expression in gastric epithelial cells is associated *H pylori* with CagA positive phenotype [49]. In our meta-analysis, no significant associations could be found among *Helicobacter pylori* positive or negative cancer patients, which is inconsistent with the finding reported by Liu et al. [37]. The discrepancy could be explained that the study conducted by Lee et al. [19] was finally included in the *Helicobacter pylori* infection subgroup analysis in our meta-analysis but not in the meta-analysis by Liu et al. revealed in their Fig. 2 [37], because the OR in the study conducted by Lee et al. [19] is oppositely strong enough (0.40) to offset the overall OR, thus the insignificant value (1.56) could be reached. At any rate, the real association between *Helicobacter pylori* infection status and IL-8 -251 A/T SNP should be further meticulously investigated in the future.

With the advent of sophisticated genotyping technologies like seminested polymerase chain reaction, TaqMan allelic discrimination test, or real-time PCR, we may witness an upsurge of genetic association studies in the future. In our meta-analysis, statistically significant finding could be noted in other genotyping technique subgroups but not in conventional PCR-RFLP subgroup. The difference should be concerned with caution. We propose that the sensitivity and specificity of those genotyping techniques need to be further explored so as to seek out the optimal approaches which could minimize the genotyping errors [5,42].

Up to now, two genome-wide association (GWA) studies related to gastric cancer have been published [50,51]. They both reported that common variants associated with the risk of esophageal squamous cell carcinoma are also associated with the risk of cardia gastric cancer, but neither of them found IL-8 to be a risk gene of gastric cancer. Our explanation of the discrepancy is that the common initial stage of those two GWA studies focuses merely on esophageal squamous cell carcinoma. Therefore, albeit they found the shared risk variants between esophageal squamous cell carcinoma and gastric cancer, they might miss those risk genes which only confer risk to gastric cancer. Thus, we advocate more genetic studies, especially GWA studies, for gastric cancer to be carried out in the near future.

Finally, the strength of our meta-analysis could be summarized as follows. We sought to find as many publications as we could by means of various searching approaches. The study that appeared to deviate from HWE was not excluded mechanically in our meta-analysis unless there are other convincing grounds for doubting the quality of the study [44]. We laid more emphasis on assessing biases across studies and pinpointing the potential sources of heterogeneity via subgroup and sensitivity analyses. We comprehensively assessed the publication biases using several means like Begg’s and Egger’s tests as well as funnel plot tests. In view of this, we convince that the results of our meta-analysis, in essence, are sound and reliable.

Certainly, there are some unavoidable limitations in our meta-analysis. Firstly, the offered information from the included studies is inconsistent. Put it another way, the information about overall gastric cancer susceptibility is predominantly provided, while more
important information about pathologic subtypes or anatomic subtypes of gastric cancer is less provided. Thus, the specific subtype results should be considered with caution. Secondly, with the merely published studies included in our meta-analysis, publication bias is very likely to occur, though no or a little statistical significance. Finally, bias is likely to be imitated in our meta-analysis. Thirdly, moderate to severe heterogeneity could be witnessed among the included studies. So as to minimize the potential bias, we designed a rigorous protocol before conducting meta-analysis, and performed a scrupulous search for published studies using explicit methods for study selection, data extraction, statistical analysis, adoption of the most appropriate genetic model and sensitivity analysis.

In conclusion, IL-8 -251 AA genotype is associated with the overall risk of developing gastric cancer and may seem to be more susceptible to overall gastric cancer in Asian populations, especially for Chinese Han population. IL-0 -251 AA genotype is more associated with the intestinal-type gastric cancer. IL-0 -251 AA genotype is not associated with Helicobacter pylori infection status in our meta-analysis.

Supporting Information

Table S1 Scales for Quality Assessment. (DOC)

Author Contributions

Conceived and designed the experiments: HX GH. Performed the experiments: BL HX. Analyzed the data: JL BL ZW JS. Contributed reagents/materials/analysis tools: BL ZW. Wrote the paper: HX GH.

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