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Interleukin 1ß-511T gene (IL1ß) polymorphism is correlated with gastric cancer in the Caucasian population: Results from a meta-analysis

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Abstract. The polymorphisms of interleukin-1ß (IL1ß) genes have been controversially correlated with gastric cancer risk. We examined all the available published studies through a meta-analysis approach. Twenty-one studies assessing the correlation between IL1ß gene polymorphisms and gastric cancer were examined: 15 studies evaluated the role of IL1ß-511T, 12 of IL1ß-31T and 6 investigated both polymorphisms. The IL1ß-511T polymorphism was correlated with an increased risk of developing gastric cancer in the global population (OR of 1.23, 95% CI 1.09-1.37, P=0.0002). The analysis of the population stratified for Caucasian and Asian ethnicities showed that the IL1ß-511T polymorphism was correlated with a statistically significant increased risk of gastric cancer in the Caucasian (OR of 1.56, 95% CI 1.32-1.84, P<0.00001), but not in the Asian population (OR of 1, 95% CI 0.85-1.16, P=0.95). An analysis of patients with the IL1ß-31T genotype did not show an increased risk of developing gastric cancer either on the overall or stratified population. The present data partially agree with the results of the two recently published meta-analyses. Our findings confirm the correlation between the IL1ß-511T allele polymorphism and gastric cancer risk in the overall population. However, this correlation is not statistically significant in the Asian, but is strongly correlated in the Caucasian subgroup. The present analysis considered a more copious sample size of cases after taking into account all the studies published recently by searching the 'PubMed' and 'MEDLINE' databases until July 2007. Hence, the present study contributes to clarify the controversial results on IL1ß polymorphisms and gastric cancer risk correlation evidencing the importance of ethnicity in the generation of the IL1ß polymorphism analysis.

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Key words: gastric cancer, interleukin 1ß gene, interleukin 1ß polymorphisms

Introduction

Gastric cancer is the fourth most common cancer in the world and the second leading cause of cancer death (1). The Gram-negative bacterium, *Helicobacter pylori*, has been classified as the definite etiological factor for gastric adenocarcinoma (2). However, of infected patients only 15-20% and <1% will develop ulcers (gastric or duodenal) or gastric adenocarcinoma, respectively (3). It is believed that bacterial and host factors such as the *Helicobacter pylori* strain virulence, environmental factors and genetic predisposition are all responsible for the different pathological outcomes (4).

The polymorphisms of genes encoding for inflammatory cytokines [notably, interleukin (IL)1ß and its endogenous receptor antagonist (IL1RN or its synonym IL1-rα), and tumor necrosis factor-α (TNF-α)] are among the host genetic factors that may play a role in determining the different patterns of *Helicobacter pylori*-induced gastric diseases (5-7).

IL1ß and IL1RN modulate the inflammatory response of the gastric mucosa and regulate gastric acid secretion (8). Moreover, IL1ß is a potent pro-inflammatory cytokine and a powerful inhibitor of gastric acid secretion, and plays an important role in initiating and amplifying the inflammatory response to the *Helicobacter pylori* infection (9-11).

Studies conducted in different ethnic populations (Caucasians and Japanese) have consistently shown that pro-inflammatory IL1ß polymorphisms are associated with more severe degrees of gastric mucosa inflammation and also with an increased prevalence of pre-cancerous lesions.

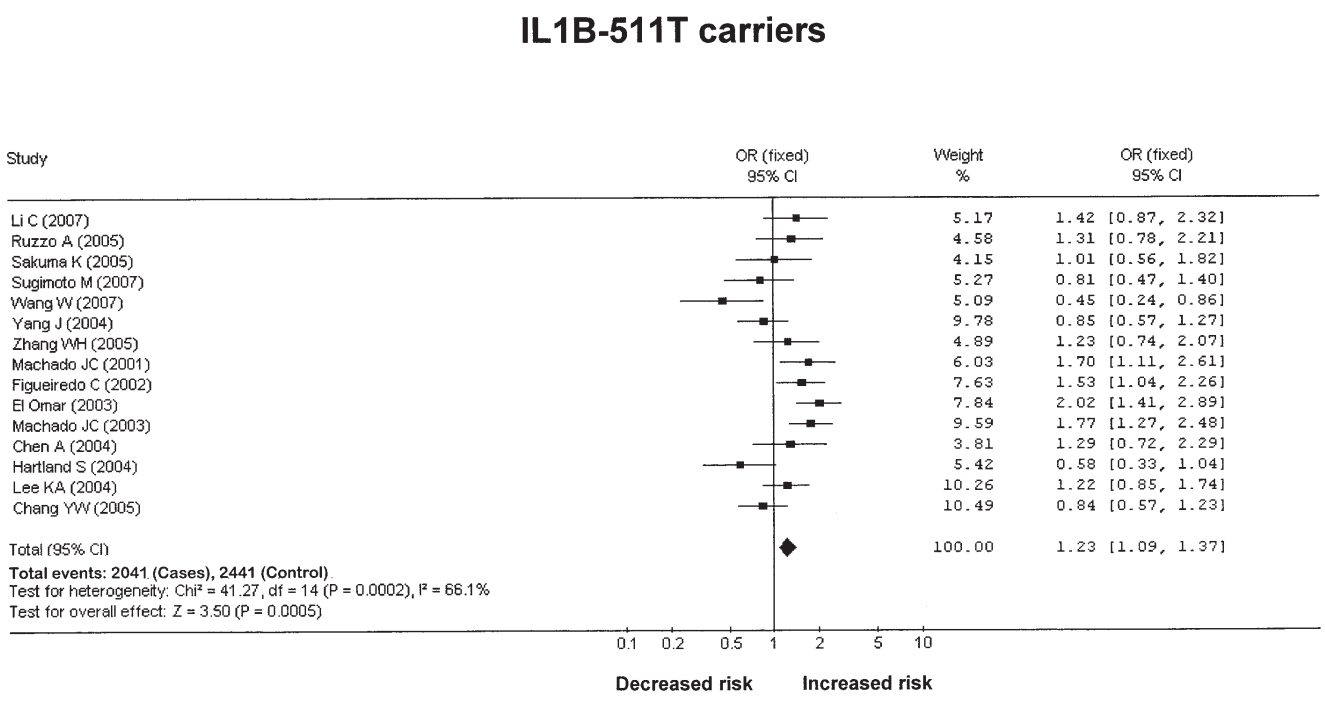

Figure 1. A forest plot for the association of IL1ß-511T carriers and gastric cancer risk in the overall population.

Taking into consideration that chronic inflammation promotes the development of cancer, a number of polymorphisms of genes encoding for pro-inflammatory cytokines have been studied and a correlation with gastric cancer risk has been found.

El-Omar *et al,* described for the first time, that polymorphisms in IL1ß were associated with gastric cancer (12). Two IL1ß single nucleotide polymorphisms (-511 C>T) and (-31 T>C) were correlated with a 2- to 3-fold increased risk of gastric cancer. Subsequent studies confirmed this correlation (6,13). Other studies described the same correlation that was, however, limited to specific histological sub-types (i.e. intestinal and diffuse) or anatomic sites (i.e. non-cardial) (6,14). On the other hand, some studies failed to find any correlation. The reasons for this discrepancy are unclear. A possible factor influencing the heterogeneity of these results may be the ethnic distribution of the population included in the studies. Genetic variations differ across ethnic groups and such differences may explain, at least in part, cancer incidence disparities among these groups. Single nucleotide polymorphisms (SNPs) within cytokine genes are differently involved in the generation of an altered expression and function of the pro-inflammatory cytokines within the different ethnic subgroups (15-17). Different cytokine networks based on an unknown unbalanced expression of different cytokines may be present in the different populations thereby disclosing a new scenario of investigations.

Socio-economic factors such as the prevalence of the *Helicobacter pylori* infection and its virulent factors, lifestyle, diet and environment for which Asian and Western populations vary may also be responsible for this discrepancy.

The aim of the present study was to perform a systematic meta-analysis of all studies published thus far by using very stringent inclusion criteria to assess the role of the IL1ß polymorphism in the pathogenesis of gastric cancer within the general population and stratified ethnic groups (Caucasians and Asians).

Materials and methods

Research strategy and study selection. We searched the 'MEDLINE', 'CENTRAL' and 'PubMed' databases (last search performed in July 2007), and reviewed cited references to identify relevant studies. Combinations of the following key words were used: gastric cancer (or stomach cancer, or gastric or stomach adenocarcinoma) and IL1, IL1ß, IL1ß-31, IL1ß-511 and polymorphisms.

In addition, supplemental bibliography was searched on the American Society of Clinical Oncology (ASCO), European Cancer Conference (ECCO) and European Society for Medical Oncology (ESMO) web-sites. The results of these searches were combined in a common set of citations from which the titles and abstracts were screened for potential qualifying studies. We restricted our review to longitudinal or case-control studies. References cited in the selected manuscripts were also considered. The literature search was performed independently by the authors, using the guidelines for reporting the meta-analysis of epidemiological studies.

Data were extracted from each study independently by each reviewer and entered onto a structured spreadsheet. No conflicting evaluations were found by the reviewers and negligible discrepancies were resolved through discussion. Major items included the year when the study was performed, study design, selection criteria of the case patients and control subjects, matching techniques, mean age, number of subjects in each group, prevalence of IL1ß, odds ratios (ORs) and 95% confidence intervals (CIs) and use of statistical adjustments.

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The general characteristics of the studies included in the analysis of the IL1ß-511T polymorphism.

Author	Recruiting time	Method	Cases	Controls	Histology	Ethnicity	HP positive
Chang YW (2005)	2000-2003	PCR-RFLP	234	434 healthy volunteers and dyspeptic patients	117 intestinal 116 diffuse 1 atypical	Asian (Korea)	172 cases 271 controls
Chen A (2004)	N.D.	PCR-RFLP	142	164 healthy volunteers	83 intestinal 46 diffuse 17 atypical	Asian (Taiwan)	100 cases 79 controls
Figueiredo C (2002)	N.D.	PCR-SSCP	221	222 chronic gastritis cancer-free subjects	116 intestinal 52 diffuse 54 atypical	Caucasian (Portugal)	All subjects HP positive
Hartland S (2004)	N.D.	PCR-RFLP	59	286 healthy volunteers	N.D.	Caucasian (UK)	98 cases 81 controls
Ruzzo A (2005)	N.D.	PCR-RFLP	138	100 healthy volunteers	76 intestinal 62 diffuse	Caucasian (Italy)	No HP positive subjects
Sakuma K (2005)	1995-1999	PCR-RFLP	140	103 healthy volunteers	70 intestinal 70 diffuse	Asian (Japan)	130 cases controls N.D.
Yang J (2004)	N.D.	PCR-RFLP	280	258 randomly selected healthy volunteers	N.D.	Asian	154 cases 164 controls
Lee KA (2004)	N.D.	PCR-RFLP	331	433 not specified cancer-free subjects	133 intestinal 188 diffuse 10 mixed	Asian	N.D.
Li C (2007)	N.D.	PCR-RFLP	143	264 healthy volunteers	N.D.	Asian (China)	74 cases 164 controls
Sugimoto M (2007)	2001-2004	PCR-RFLP	105	172 healthy volunteers	81 intestinal 24 diffuse	N.D.	105 cases 172 controls
Wang W (2007)	N.D.	ALM-ASA	97	141 healthy volunteers	97 mixed	Asian (China)	N.D.
Machado JC (2003)	N.D.	PCR-SSCP	287	306 healthy volunteers	128 intestinal 90 diffuse	Caucasian (Portugal)	176 cases
Zang WH (2005)	2002-2005	PCR	154	166 healthy controls	N.D.	China	N.D.
Machado JC (2001)	N.D.	PCR-SSCP	152	220 healthy volunteers	76 intestinal 37 diffuse 39 typical	Caucasian (Portugal)	N.D.

PCR, polymerase chain reaction; PCR-SSCP, PCR-single-strand conformational polymorphism; ALM-ASA, adapter ligation-mediated allele-specific amplification; PCR-RFLP, PCR-restriction fragment length polymorphism; HP, *Helicobacter pylori*, N.D., not determined.

Studies testing the association between IL1ß-31 and/or IL1ß-511 gene polymorphisms and gastric cancer were considered if all the following inclusion criteria were found: a) the study assessed the correlation between gastric cancer and at least one of the polymorphisms cited above; b) the study population included a population with and without gastric cancer; c) control subjects matched with case patients for age and gender; d) the study reported the relative risk with 95% CIs (rejecting the null hypothesis), the odds ratio or data for their calculation; e) only full-text manuscripts were included (even if a complete search in the abstract book of the main international conferences was performed) and f) the study was published in English.

Studies were excluded when the complete data were not available or in the case of a duplicate publication of results or of conference abstracts. Moreover, manuscripts with a clear bias of accrual (for example, a control population from a region different from that of the patients) were excluded.

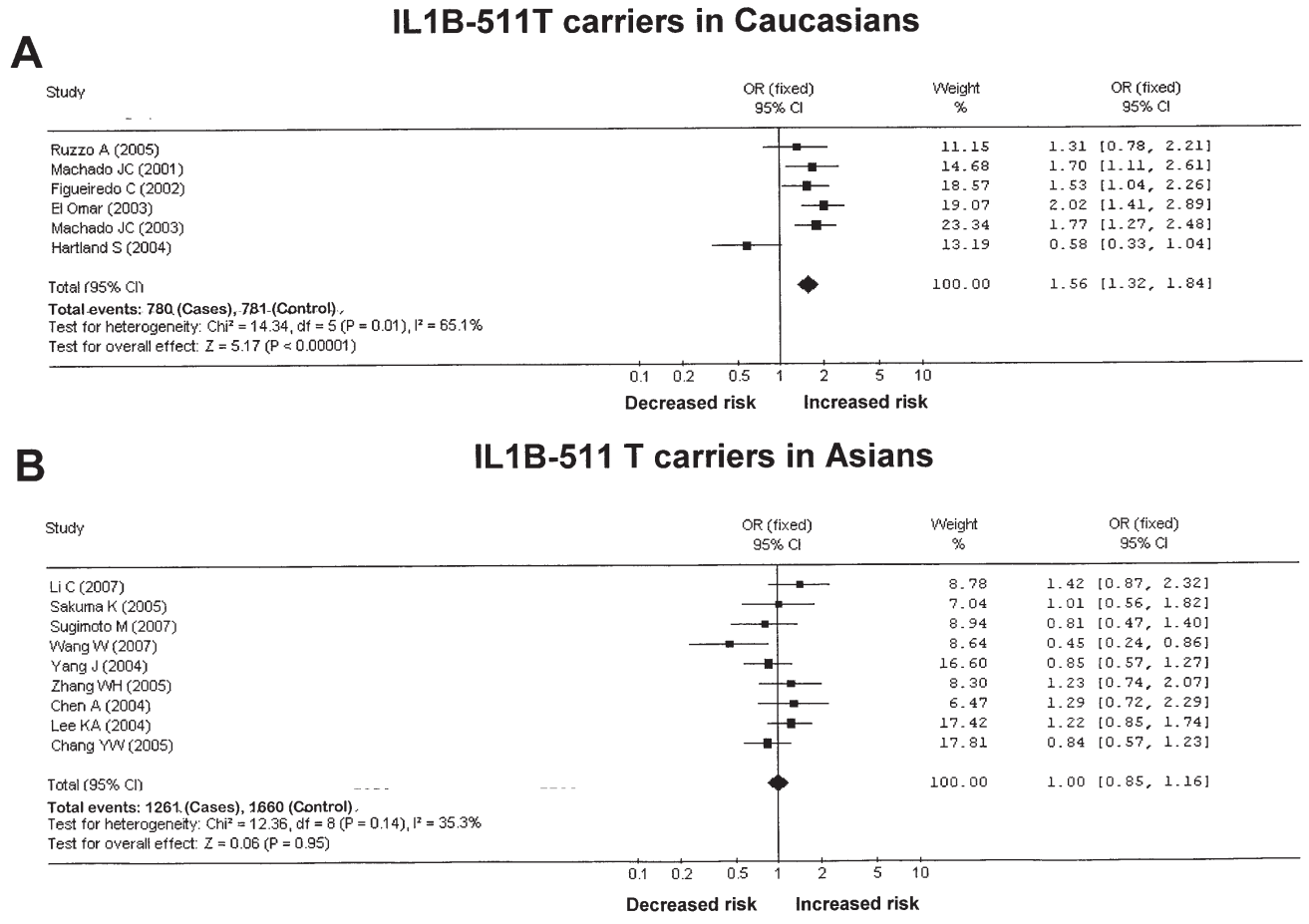

Figure 2. (A) A forest plot for the association of IL1ß-511T carriers and gastric cancer risk in Caucasians. (B) The forest plot for the association of IL1ß-511T carriers and gastric cancer risk in Asians.

Statistical analysis. All analyses were performed using the review manager 4.2.10 software (available from The Cochrane Collaboration at http//www.cochrane.org). The Mantel-Haenszel method for fixed effects (19) and the DerSimonian-Laird method for random effects were used to estimate pooled ORs. We tested the heterogeneity of the included studies with Q statistics and the extent of the inconsistency between results with I2 statistics 22. In the absence of heterogeneity between the studies, the Mantel-Haenszel and the DerSimonian-Laird methods give very similar results. We report fixed-effect estimate, as the fixed effects are more robust in meta-analysis calculations when there are small numbers of events. Data are shown as ORs with 95% CIs, with two-tailed P-values and statistical significance was set at P<0.05 (two-tailed).

Results

The literature search was updated to July 2007. The full-text of the retrieved studies were examined to assess their suitability for meta-analysis according to the inclusion criteria.

Twenty-one studies (5,6,7,14,21-34) investigated the association between IL1ß-511 and/or -31 polymorphisms and gastric cancer risk and met the inclusion criteria.

Data from 15 studies, including 2041 cases and 2441 controls, were evaluated for the meta-analysis of IL1ß-511 and from 12, including 1535 cases and 2585 controls, for that of IL1ß-31. Six of the previous studies investigated the two polymorphisms. The characteristics of these studies are reported in Tables I and II.

All the studies had a case-control design. The cases were defined after the histopathological diagnosis of gastric cancer and controls were recruited among the following subgroups: healthy volunteers, chronic gastritis and dyspeptic patients, healthy blood-donor volunteers and not specified cancer-free patients. In all the studies, validated genotyping methods were used for the genetic determination of polymorphisms. The selected studies were conducted in the populations of two different ethnicities: 9 involved Caucasians and 12 Asians.

The IL1ß-511T polymorphism and gastric cancer risk. The IL1ß-511T polymorphism was associated with an increased risk of developing gastric cancer in the global population (OR of 1.23, 95% CI 1.09-1.37). As shown in Fig. 1, individuals carrying the IL1ß-511T allele have a significantly higher gastric cancer risk (P=0.0002).

The analysis of the populations stratified into Caucasian and Asian ethnicities (including 1261 cases in Asians and 780 in Caucasians) showed that the IL1ß-511T polymorphism was associated with a statistically significant increased risk of gastric cancer in the Caucasian (OR of 1.56, 95% CI 1.32-1.84, P<0.00001), but not in the Asian population (OR of 1, 95% CI 0.85-1.16, P=0.95) (Fig. 2A and B, respectively).

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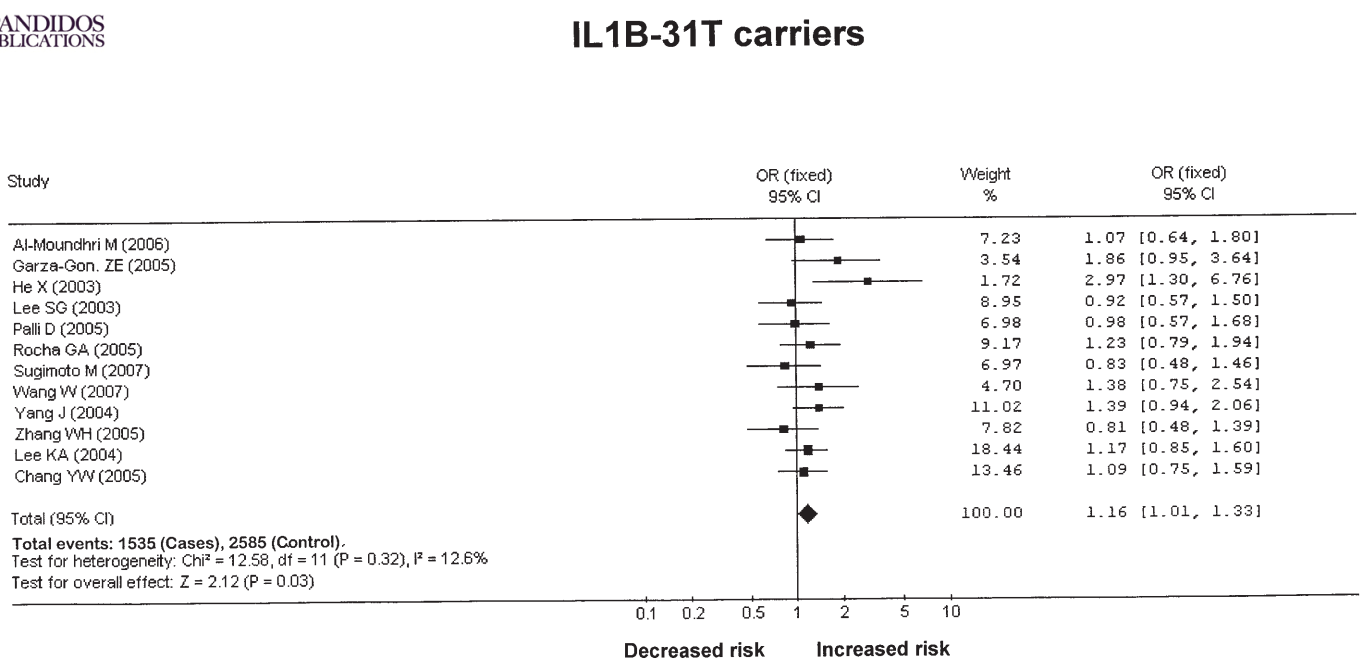

Figure 3. A forest plot for the association of IL1ß-31T carriers and gastric cancer risk in the overall population.

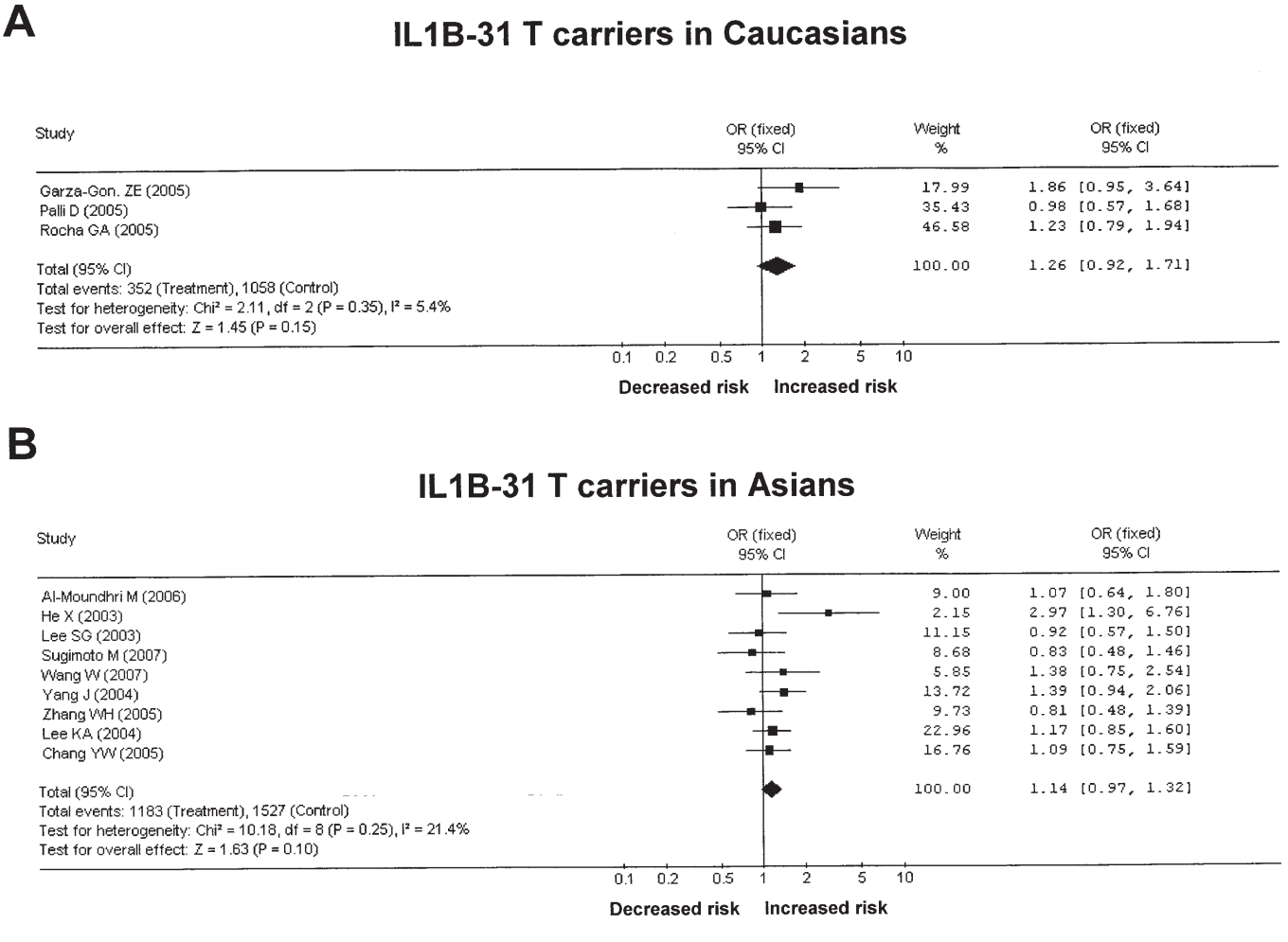

Figure 4. (A) A forest plot for the association of IL1ß-31T carriers and gastric cancer risk in Caucasians. (B) The forest plot for the association of IL1ß-31T carriers and gastric cancer risk in Asians.

Table II. The general characteristics of the studies included in the analysis of the IL1ß-31T polymorphism.

Author	Recruiting time	Method	Cases	Controls	Histology	Ethnicity	HP positive
Chang YW (2005)	2000-2003	PCR-RFLP	234	434 healthy asymptomatic volunteers and dyspeptic patients	117 intestinal 116 diffuse 1 atypical	Asian (Korea)	172 cases 271 controls
Garza-Gonzalez E (2005)	N.D.	PCR-RFLP	63	215 dyspeptic patients	29 intestinal 34 diffuse	Caucasian (Mexico)	31 cases 116 controls
Lee SG (2003)	1999-2001	PCR-RFLP	172	190 not specified cancer-free subjects	28 intestinal 153 diffuse 9 unclassified	Asian (Korea)	N.D.
Rocha GA (2005)	N.D.	PCR-RFLP	166	541 healthy blood donors	N.D.	Caucasian (Brazil)	166 cases 367 controls
Yang J (2004)	1998-2000	PCR-RFLP	280	258 randomly selected healthy volunteers	N.D.	Asian (China)	154 cases 164 controls
He X (2003)	N.D.	PCR-RFLP	50	50 not specified cancer-free subjects	N.D.	Asian (China)	N.D.
Lee KA (2004)	N.D.	PCR-RFLP	331	433 not specified cancer-free subjects	133 intestinal 188 diffuse 10 mixed	Asian (Korea)	N.D.
Palli D (2005)	1995-1997	PCR-RFLP	185	546	36 intestinal type	Caucasian (Italy)	130 cases N.D. controls
Al-Moundhri MS (2006)	2002-2005	PCR	118	245	63 intestinal 55 diffuse	Arab	42 cases 46 controls
Sugimoto M (2007)	2001-2004	PCR-RFLP	105	172 healthy volunteers without any gastroduodenal lesions	81 intestinal 24 diffuse	N.D.	105 cases 172 controls
Wang W (2007)	N.D.	ALM-ASA	97	141	97	Asian (China)	N.D.
Zang WH (2005)	2002-2005	PCR	154	166 healthy blood donors	N.D.	China	N.D.
El-Omar EM (2003)	N.D.	PCR-SSCP	314	212 healthy blood donors	N.D.	USA	214 cases

PCR-RFLP, PCR-restriction fragment length polymorphism; PCR-SSCP, PCR-single-strand conformational polymorphism; ALM-ASA, adapter ligation-mediated allele-specific amplification; HP, *Helicobacter pylori*, N.D., not determined.

The IL1ß-31T polymorphism and gastric cancer risk. The overall analysis of patients with the IL1ß-31T genotype did not show an increased risk of developing gastric cancer (OR of 1.16, 95% CI 1.01-1.33, P=0.32) (Fig. 3).

Therefore, we performed a stratified analysis according to ethnicity (including 1183 cases in Asians and 352 in Caucasians) but there was again no significant correlation. These data suggested that the IL1ß-31T genotype is quite independent from ethnicity. In Caucasians, the OR was 1.26, 95% CI 0.92-1.71, P=0.15 vs. 1.14, 95% CI 0.97-1.32, P=0.10 in Asians (Fig. 4A and B, respectively).

Discussion

The variable range of gastric cancer incidence across world populations may be partially explained by differences in genetic susceptibility.

Since El-Omar *et al* (12) first focused on the possible relationship between gastric cancer risk and polymorphisms in genes encoding the IL1ß gene, several reports have been published examining this hypothesis (5,6,7,14,21-34). However, the overall results on the association between IL1ß polymorphisms and gastric cancer risk are conflicting.

For this reason we were prompted to the present meta-analysis in order to derive the estimate of gastric cancer risk associated with the IL1ß-511 and -31 polymorphism status. Another objective was to perform an updated meta-analysis through the revision of the literature to July 2007 thereby covering the temporal bias of 1 year from the previously published meta-analyses.

IL1ß modulates the inflammatory response of the gastric mucosa and regulates gastric acid secretion (8). Moreover, IL1ß is a potent pro-inflammatory cytokine and a powerful inhibitor of gastric acid secretion playing an important role in

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and amplifying the inflammatory response to *Helicobacter pylori* infection (9-11).

Studies carried out in different ethnic populations showed that pro-inflammatory IL1ß polymorphisms were associated with more severe degrees of gastric mucosa inflammation and with an increased prevalence of precancerous lesions.

Considering that chronic inflammation promotes the development of cancer, a number of pro-inflammatory cytokine gene polymorphisms have been studied and have been demonstrated to associate with gastric cancer risk.

In our meta-analysis, data from 21 published case-control studies that met the inclusion criteria were analysed.

We observed that the IL1ß-511T polymorphism is associated with a statistically significant increased risk of developing gastric cancer in the global population. Ethnicity was identified as a source of heterogeneity and the population was stratified for Caucasian and Asian populations. Notably, the derived analysis showed that the IL1ß-511T polymorphism was associated with a statistically significant increased risk of gastric cancer only in Caucasians.

The reason for this ethnic-specific effect may be the high prevalence of the IL1ß-511T allele in the Asian versus the Caucasian population. The typical frequencies of the two studied polymorphisms in the control populations are different: for IL1ß-511T 0.33 and 0.51 and for IL1ß-31C 0.33 and 0.50 in Caucasians and Asians, respectively (35).

Conversely, the different frequency of IL1ß polymorphisms among the two ethnicities creates difficulty in analysing their role in the pathogenesis of gastric cancer.

On the other hand, the overall analysis of patients with the IL1ß-31T genotype did not show an increased risk of developing gastric cancer. The IL1ß-31T genotype is quite independent for ethnicity and did not confer an increased risk of developing gastric cancer in either subgroup.

In the literature, a nearly complete linkage disequilibrium between IL1ß-31 and -511 is described in Asians and Caucasians even if the pattern of haplotype related to the risk of gastric cancer (IL1ß-31T/IL1ß-511C) is opposite (IL1ß-511T/IL1ß-31 C) (12,25,36-38).

Although the IL1ß-511T is in a tight linkage disequilibrium with IL1ß-31C, a discrepancy can be found in the reported results. It is unclear why the same association was not found for the two polymorphisms. Several sources of bias against the -31 locus are present but have not been well-identified thus far. Among them is the smaller sample size used in the IL1ß-31 studies.

Previous studies regarding the association between IL1ß polymorphisms and risk of gastric cancer have produced conflicting results (6,12-14). Some of them showed an association between IL1ß polymorphisms and gastric cancer risk but other studies failed to demonstrate the latter.

A recent meta-analysis by Wang *et al* found that the IL1ß-511T was associated with an increased risk of developing gastric cancer, especially in the intestinal type, but the IL1ß-31C was not (39). The conclusion on the IL1ß-511T carrier is consistent with most of the related studies as well as with the present meta-analysis.

Camargo *et al* reported that individuals carrying the IL1ß-511T allele have a significantly higher gastric cancer risk versus those with the C/C genotype. A significant correlation was found between IL1ß-511T and gastric cancer risk in the Caucasians, but not in the Asians (35). These results are consistent with those reported in the present meta-analysis.

Kamangar *et al* did not find an overall association of IL1ß-511T and -31C alleles with a risk of gastric cancer (40). Notably, the authors reported significant heterogeneity among the study results.

In conclusion, the heterogeneous results are due to different causes that can be grouped into biological and/or socio-economic reasons. Among the biological factors, ethnicity plays a key role. Moreover, other gastric cancer risk factors such as the prevalence of the *Helicobacter pylori* infection and its virulent factors, lifestyle, diet and environment for which Asian and Western populations differ, may be additional causes of this discrepancy.

The main causes of the discrepancy found in the two ethnic subgroups in our study are: i) the gastric anatomic subsite (cardia versus non-cardia), ii) histology (intestinal versus diffuse histotype), iii) tumor misclassification by histology or anatomic site, iv) genotyping inaccuracy and v) inadequate control groups. Finally, the small number of studies and consequently a limited statistical power is another limit, particularly for the IL1ß-31 allele.

Our updated meta-analysis, although affected by the common bias of each epidemiological study, partially supports the results of the two recently published meta-analyses as well as of previous studies. Our results confirm the association between IL1ß polymorphisms and gastric cancer risk, particularly concerning the association of the IL1ß-511T allele on the overall population and more specifically on the Caucasian subgroup.

Therefore, the present study contributes to clarify the actual controversial results of the IL1ß polymorphisms and gastric cancer risk association.

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