Interleukin 1 beta (IL1B) promoter polymorphism and cancer risk: evidence from 47 published studies

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Interleukin 1β (IL-1β) is a pro-inflammatory cytokine against infection, playing an important role in the pathogenesis of cancers. The -31T/C polymorphism of the interleukin 1β gene (IL1B) has been implicated in cancer risk through its influence on the IL1B transcription. However, results from studies are conflicting. To clarify the association, a meta-analysis was performed for 112 cases and 14 415 controls from 47 published case–control studies. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of the association. No significant associations were observed for total cancer from all the comparisons. Through the stratified analyses, there was a statistically significant decreased risk of hepatocellular cancer in carriers of the C allele compared to non-carriers (CC versus TT: OR = 0.87, 95% CI: 0.77–0.98, \( P_{\text{heterogeneity}} = 0.103 \); TC versus TT: OR = 0.77, 95% CI: 0.62–0.95, \( P_{\text{heterogeneity}} = 0.734 \); TC + CC versus TT: OR = 0.74, 95% CI: 0.61–0.91, \( P_{\text{heterogeneity}} = 0.472 \)). Similarly, decreased risk was observed for gastric cancer of the C/C genotype compared with the T/T genotype (OR = 0.87, 95% CI: 0.77–0.98, \( P_{\text{heterogeneity}} = 0.103 \)). Using the recessive model, a significantly decreased risk was observed for gastric cancer (OR = 0.88, 95% CI: 0.80–0.97, \( P_{\text{heterogeneity}} = 0.158 \)), European population (OR = 0.84, 95% CI: 0.73–0.97, \( P_{\text{heterogeneity}} = 0.070 \)) and positive infection-matched studies (OR = 0.75, 95% CI: 0.60–0.94, \( P_{\text{heterogeneity}} = 0.220 \)); however, an increased risk was found for breast cancer (OR = 1.34, 95% CI: 1.18–1.61, \( P_{\text{heterogeneity}} = 0.116 \)). Although some modest bias could not be eliminated, this meta-analysis suggests that the IL1B -31C allele is a low-penetrance protective factor for the development of cancer, in particular for that associated with infection.

Materials and methods

Identification of eligible studies

Electronic literature search was performed with PubMed, EMBASE and Cochrane Library for all relevant reports (the last search update was as of December 23, 2010), using the key words ‘interleukin-1’ or ‘IL-1’, ‘polymorphism’, ‘tumour’ and ‘carcinoma’. The search was limited to English language papers and human associated studies. In addition, studies were identified by a manual search of the reference lists of reviews and retrieved studies. When more than one of the same or overlapping population by different investigators or overlapping data by the same authors were found, only the most recent or complete study was used for this meta-analysis. Studies, regardless of sample size, were enrolled if they met the following inclusion criteria: (i) a study of the IL1B-31T/C polymorphism and cancer risk; (ii) a case–control study meeting the Hardy–Weinberg equilibrium in the control population (17–22). In light of the extensive role of polymorphisms in IL1B, a pooled analysis is needed to accumulate data from different studies and to provide better evidence for or against that association. Therefore, we performed a meta-analysis to evaluate the association of IL1B-31 with cancer susceptibility in all eligible case–control studies.

Discussion

Introduction

Inflammation has long been considered as an important factor in the pathogenesis of many human cancers (1,2). Interleukins (ILs) are pro-inflammatory cytokines produced by monocytes, macrophages and epithelial cells, which play important roles in the defence against infection. The IL-1 family, including IL-1α, IL-1β and IL-1 receptor antagonist (IL-1Ra) (3), are an important component of the innate immune system. Interleukin 1β (IL1B) is not only an important host genetic factor but also a key pro-inflammatory cytokine (4), which can regulate the expression of several molecules involved in inflammation. For example, the interleukin 1 β gene (IL1B) -31T/C substitution located in the TATA box motif in the promoter region of the gene IL1B has been found to markedly affect the binding of several transcription factors (5–7) and thereby affect the transcription activity of IL1B (6). It is not surprising that the two functionally important polymorphisms in the promoter region of IL1B -31T/C (rs1143627) and -511C/T (rs16944) were associated with the risk of gastric cancer (5). Furthermore, a number of epidemiological studies have investigated the associations between these polymorphisms and different cancers, such as the lung (8), breast (9), liver (10), colorectal (11) and ovarian (12) cancers. However, the results remained controversial (13–15) partially because of small sample size, the difference in the genotype distribution by ethnicity (16), study design, assay characteristics and so on. Furthermore, several studies have revealed that IL1B-31T allele was closely linked to the -511C in European and Asian population (17–22). In light of the extensive role of polymorphisms in IL1B, a pooled analysis is needed to accumulate data from different studies and to provide better evidence for or against that association. Therefore, we performed a meta-analysis to evaluate the association of IL1B-31 with cancer susceptibility in all eligible case–control studies.

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Statistical analysis
A meta-analysis was used to examine the overall association of the IL1B-31 with the risk of cancer by ORs with 95% confidence intervals (CIs). As compared to the wild-type T/T homozygote, the risk of carriage of the C allele (i.e. T/C and C/C genotypes) on cancers was estimated, followed by evaluating the risk of T/C + C/C versus T/T and of C/C versus T/C + T/T on cancer in dominant and recessive effects, respectively. Stratified analyses were also performed by ethnicity, research methods and cancer types (if only one cancer type contained fewer than three individual studies it was combined into the ‘Other Cancers’ group).

The statistical significance of the pooled OR was determined with the Z-test, and a P-value of <0.05 was considered significant. Heterogeneity across the studies was evaluated by chi-square test based on Q statistic test (24) and was considered significant if P < 0.1. A fixed-effect model using the Mantel–Haenszel method and a random-effects model using the DerSimonian and Laird method were used to pool the results (25), and the fixed-effect model was used as well when there was no heterogeneity across results of the studies, or the random-effect model was used. Moreover, a sensitivity analysis, by which a single study in the meta-analysis was deleted each time to determine the influence of the individual data set to the overall pooled OR, was performed to assess the stability of the results. To test the publication bias, Funnel plots and Egger’s linear regression test was applied (26). The Hardy–Weinberg equilibrium was also tested by the chi-square test for goodness of fit using a web-based program (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). All statistical tests for this meta-analysis were performed with STATA version 10.0 (Stata Corporation, College Station, TX, USA), the Review Manager Version 4.2 (The Cochrane Collaboration, Oxford, UK).

Results
Characteristics of studies
A total of 47 eligible studies met the preset inclusion criteria, in which 11 125 cases and 14 415 controls were included for the pooled analysis. All studies were case–control studies, including 26 studies on gastric cancer, 4 on hepatocellular cancer, 4 on breast cancer and 13 on those categorised into the other cancers. There were 25 studies of Asian descendents and 21 of European descendents and one with mixed ethnicity (27). Cancers were diagnosed histologically or pathologically in most studies. The TaqMan assay and polymerase chain reaction–restriction fragment length polymorphism were performed in 12 and 17 studies, respectively. In addition, most of the controls were sex and age-matched for the case groups, of which 29 were population based and 18 were hospital based. Besides, seven studies investigated the interactions between the polymorphism and infection status matched case–control study (18, 20, 22, 27–30). The genotype distributions among the controls of all studies were not deviated from the Hardy–Weinberg equilibrium.

Meta-analysis
Wide variation of IL1B-31T allele frequencies across different ethnicities was observed. The frequency of T allele was 50.54% (95% CI: 46.78–54.29) among Asian controls, which was significantly lower than that in European controls (58.06%; 95% CI: 52.48–63.63, P = 0.022) as shown in Figure 1.

Overall, there was no association between IL1B-31T/C and risk of cancer for any comparison. However, for the data from homozygote comparison, subgroup analysis revealed that there were significantly decreased risks of gastric cancer (OR = 0.87, 95% CI: 0.77–0.98, Phet = 0.103) and hepatocellular cancer (OR = 0.68, 95% CI: 0.52–0.89, Phet = 0.172). Decreased risks were also observed in the subgroup hepatocellular cancer (OR = 0.77, 95% CI: 0.62–0.95, Phet = 0.734) for the heterozygote comparison (TC versus TT). Similarly, decreased risks were also observed in the subgroup of hepatocellular cancer (OR = 0.74, 95% CI: 0.61–0.91, Phet = 0.472) for dominant model comparison (TC + CC versus TT). Conversely, for recessive model comparison (CC versus TT + TC), decreased risks were also observed in gastric cancer (OR = 0.88, 95% CI: 0.80–0.97, Phet = 0.158) and ethnicity of European population (OR = 0.84, 95% CI: 0.73–0.97, Phet = 0.070). However, increased risk was observed for the breast cancer subgroup (OR = 1.34, 95% CI: 1.18–1.61, Phet = 0.116) as summarised in Table I.

Gene–environment interaction
The genotype distribution of -31T/C among cases and infection-matched controls was available in seven studies that investigated gastric cancer infected by Helicobacter pylori and hepatocellular cancer infected by hepatitis C or hepatitis B virus. Carriers of the T allele had higher cancer risk (OR = 0.75, 95% CI: 0.60–0.94, Phet = 0.220) among infection-matched studies showing infection positive rather than those infection negative as illustrates in Table I and Figure 2.

Test of heterogeneity
There was significant heterogeneity across the studies in overall comparisons. For this, the source of heterogeneity was explored for the heterozygote comparison (TC versus TT) by cancer type, ethnicity and source of controls. Cancer type [χ² = 10.73, degrees of freedom (d.f.) = 3, P = 0.013] but not ethnicity (χ² = 2.25, d.f. = 1, P = 0.134) and source of controls (χ² = 0.75, d.f. = 1, P = 0.387) contributed substantially to that heterogeneity.

Sensitivity analyses
Sensitivity analysis revealed that four independent studies were the main source of heterogeneity, two were gastric cancer-related studies (5, 27) and two studies were related cervical cancer (31) and chronic lymphocytic leukaemia (32). The heterogeneity was decreased when these four studies were removed (CC versus TT: Phet = 0.126, TC versus TT: Phet = 0.232, TC versus TT: Phet = 0.232, TC + CC versus TT: Phet = 0.199, CC versus TT + TC: Phet = 0.191). In addition, no other single study was found to impact the pooled OR as indicated by sensitivity analyses.
Table I. Stratified analyses of the IL1B-31T/C polymorphism on cancer risk

<table>
<thead>
<tr>
<th>Variables</th>
<th>n²</th>
<th>Cases/controls</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>46</td>
<td>0.92 (0.83–1.03)</td>
<td>0.002</td>
<td>0.97 (0.93–1.03)</td>
<td>0.002</td>
<td>0.97 (0.93–1.03)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Cancer type</td>
<td>25</td>
<td>0.87 (0.77–0.98)</td>
<td>0.03</td>
<td>0.82 (0.73–0.91)</td>
<td>0.04</td>
<td>0.82 (0.73–0.91)</td>
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<tr>
<td></td>
<td></td>
<td>12</td>
<td>0.87 (0.81–0.94)</td>
<td>0.02</td>
<td>0.79 (0.72–0.86)</td>
<td>0.01</td>
<td>0.79 (0.72–0.86)</td>
<td>0.01</td>
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<tr>
<td></td>
<td></td>
<td>14</td>
<td>0.84 (0.78–0.90)</td>
<td>0.01</td>
<td>0.77 (0.70–0.83)</td>
<td>0.00</td>
<td>0.77 (0.70–0.83)</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13</td>
<td>0.85 (0.81–0.90)</td>
<td>0.01</td>
<td>0.78 (0.72–0.84)</td>
<td>0.01</td>
<td>0.78 (0.72–0.84)</td>
<td>0.01</td>
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<tr>
<td></td>
<td></td>
<td>7</td>
<td>0.89 (0.85–0.93)</td>
<td>0.00</td>
<td>0.82 (0.78–0.86)</td>
<td>0.00</td>
<td>0.82 (0.78–0.86)</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>0.88 (0.83–0.93)</td>
<td>0.00</td>
<td>0.81 (0.76–0.86)</td>
<td>0.00</td>
<td>0.81 (0.76–0.86)</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6</td>
<td>0.86 (0.81–0.91)</td>
<td>0.00</td>
<td>0.81 (0.76–0.86)</td>
<td>0.00</td>
<td>0.81 (0.76–0.86)</td>
<td>0.00</td>
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<tr>
<td></td>
<td>Methods</td>
<td>PCR, Taqman</td>
<td>12</td>
<td>0.84 (0.77–0.91)</td>
<td>0.01</td>
<td>0.78 (0.72–0.84)</td>
<td>0.01</td>
<td>0.78 (0.72–0.84)</td>
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<tr>
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<td>PCR-CTPP</td>
<td>7</td>
<td>0.88 (0.83–0.93)</td>
<td>0.00</td>
<td>0.81 (0.76–0.86)</td>
<td>0.00</td>
<td>0.81 (0.76–0.86)</td>
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<tr>
<td></td>
<td></td>
<td>Sequencing</td>
<td>17</td>
<td>0.89 (0.85–0.93)</td>
<td>0.00</td>
<td>0.82 (0.78–0.86)</td>
<td>0.00</td>
<td>0.82 (0.78–0.86)</td>
</tr>
<tr>
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<td>Source of controls</td>
<td>Hospital based</td>
<td>12</td>
<td>0.89 (0.85–0.93)</td>
<td>0.00</td>
<td>0.82 (0.78–0.86)</td>
<td>0.00</td>
<td>0.82 (0.78–0.86)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Population based</td>
<td>6</td>
<td>0.88 (0.83–0.93)</td>
<td>0.00</td>
<td>0.81 (0.76–0.86)</td>
<td>0.00</td>
<td>0.81 (0.76–0.86)</td>
</tr>
<tr>
<td></td>
<td>Positive-matched</td>
<td>4</td>
<td>0.86 (0.81–0.91)</td>
<td>0.00</td>
<td>0.81 (0.76–0.86)</td>
<td>0.00</td>
<td>0.81 (0.76–0.86)</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>Negative-matched</td>
<td>4</td>
<td>0.88 (0.83–0.93)</td>
<td>0.00</td>
<td>0.81 (0.76–0.86)</td>
<td>0.00</td>
<td>0.81 (0.76–0.86)</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Publication bias

Begg’s funnel plot and Egger’s test were performed to assess the publication bias of the currently available literature. The shape of the funnel plots did not reveal any evidence for obvious asymmetry in all comparison models. Then, the Egger’s test was used to provide statistical evidence for funnel plot symmetry. The results still did not show any evidence of publication bias (t = −1.14, P = 0.259 for TC versus TT; Figure 3).

Discussion

In this meta-analysis, the ILIB-31T/C polymorphism was not associated with increased risk for developing cancers of interest. However, results from stratified analyses by cancer type indicated that the carriage of the C variant allele (i.e. TC and CC) was associated with decreased risk of hepatocellular cancer, that carriers of the T allele (i.e. TT and TC) had increased risk of cancer type of gastric cancer and ethnicity of European population. Given the important roles of IL-1β in the regulation of the expression of several molecules involved in inflammation, it is possible that ILIB-31T/C polymorphism may modulate the risk of the development of cancer.

It is well known that IL-1 expression is elevated in human breast cancer, colon cancer, lung cancer, head and neck cancers and melanomas, and tumour patients with excessive IL-1 expression have worse prognosis than those without (33,34). In the case of ILIB, ILIB-31T/C allele has been found to have significantly higher ILIB expression than ILIB-31C, resulting in increased risk of developing cancer (33–37). In the present study, a significant association was observed between the -31T/C polymorphism and hepatocellular cancer but not breast cancer, suggesting that ILIB-31T/C polymorphism plays different role in the pathogenesis of different cancer types. For gastric and hepatocellular cancers, infection caused by bacteria or virus plays an important role in the carcinogenic process (38–44) as indicated in the present study by recessive model comparison among positive infection-matched studies. Moreover, three hepatocellular cancer studies being enrolled were all infection-matched, demonstrating that cancer risk associated with the ILIB-31T/C can be enhanced by bacterial or viral infection.

However, results derived from this meta-analysis should be interpreted with caution. First of all, although all eligible studies were summarised, the total sample size might be not enough to make a convincing conclusion. When stratified analysis of tumour type, ethnicity or infection status was performed, the number of each subgroup seems to be smaller. Second, there was no further evaluation of potential
gene–gene interactions and gene–environment interactions due to the lack of the original data from the studies. And last, the number of published studies was not enough for a comprehensive analysis, particularly for any kind of the cancers. Despite these limitations, this meta-analysis has some advantages. For example, the number of cases and controls through the pooled studies could significantly increase statistical power of the analysis. In addition, no publication bias was detected.

In conclusion, this meta-analysis suggests that the \(IL1B\)-31T/C polymorphism may contribute to genetic susceptibility of infection-related cancer, such as gastric cancer and liver cancer. However, further studies would be needed to clarify the possible roles of the \(ILB\)-31T/C polymorphisms in the aetiology of cancer.

Supplementary data
Supplementary Table 1 is available at Mutagenesis Online.

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References


