Association of Interleukin-10 -1082A>G (rs1800896) Polymorphism with Predisposition to Breast Cancer: a Meta-Analysis based on 17 Case-Control Studies

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SUMMARY

INTRODUCTION: The association between the between IL-10 -1082A>G (rs1800896) polymorphism and breast cancer has been evaluated by several number case-control studies. However, these studies might be underpowered to reveal the true association.

OBJECTIVE: We have performed a comprehensive meta-analysis to investigate the association IL-10 -1082A>G polymorphism and breast cancer.

MATERIALS AND METHODS: A systematic literature search was conducted using PubMed, Google Scholar, and Web of Science up to September 20, 2017. Data was analysed with CMA software to identify the strength of the association by pooled odds ratios (ORs) with corresponding 95% confidence intervals (CIs).

RESULTS: A total of 17 case-control studies involving 3275 cases and 3416 controls obtained from database searches were examined. Overall, there was no significant association between IL-10 -1082A>G polymorphism and breast cancer risk under all genetic models. No significant publication bias was found for the five genetic models (G vs. A: OR = 1.184, 95% CI = 0.895-1.180, p= 0.230; GG vs. AA: OR = 1.430, 95% CI = 0.927-2.204, p= 0.106; GA vs. AA: OR = 0.966, 95% CI = 0.765-1.221, p= 0.774; GG+GA vs. AA: OR = 0.957, 95% CI = 0.697-1.314, p= 0.786; and GG vs. GA+AA: OR = 1.221, 95% CI = 0.981-1.518, p= 0.073). Moreover, there was no significant association between the IL-10 -1082A>G polymorphism and breast cancer risk by ethnicity.

CONCLUSION: Our findings indicated that IL-10 -1082A>G (rs1800896) polymorphism might not be a risk factor for the development of breast cancer.

INTRODUCTION

Breast cancer is one of the most commonly diagnosed invasive malignancies. Breast cancer is the second most common cancer-related death in women worldwide and accounts for 15.4% of cancer-related deaths in women. The pathogenesis of breast cancer is multifactorial. Hereditary breast cancer accounts for only 5-10% of all breast cancer cases and germline mutations with the two major breast cancer susceptibility genes BRCA1 and BRCA2, being responsible approximately for 2-3% of all cases. Besides gene tests to identification of high-risk BRCA1 or BRCA2 mutations carriers, the ability to predict breast cancer development, is not well established yet. The findings suggest that accumulation of several polymorphic variants is responsible for elevated risk of breast cancer. However, the association of genetic variations with the clinical characteristics and prognosis in breast cancer has not been fully identified.

The human interleukin 10 gene is a steroid hormone receptor gene located on chromosome 6 at 6q25.1. It contains eight exons spanning 295 kb. The IL-10 promoter is highly polymorphic and three most common SNPs, including -1082, -819, and -592, within this region have been correlated with IL-10 production. Several epidemiological studies have evaluated IL-10 -1082 polymorphism and its association with breast cancer. However, the effects of polymorphisms in rs2077647, rs2228480 and rs3798577 were also controversial. It is clear that the number of studies, time of analysis and new studies included in a meta-analysis directly influences the credibility and stability of the findings. Therefore, we have performed this systematic review and meta-analysis to more accurately assess the association between IL-10 -1082A>G (rs1800896) polymorphism and breast cancer risk, using more recent published studies.

MATERIALS AND METHODS

Search Strategies

A computerized literature search of different databases, including PubMed, Web of Science, EMBASE, China National Knowledge Infrastructure (CNKI), China Biology Medicine (CBM) and Google Scholar was conducted up to September 20, 2017. The search strategy identified all possible studies using combinations of the following terms and keywords:

- Breast cancer
- interleukin 10
- IL-10 gene
- -1082A>G
- rs1800896
- polymorphism
- variant
- mutation

Furthermore, we have manually screened the bibliographies of relevant articles and reviews for additional studies that were not captured by the database search. Publications in both English and Chinese languages were included, and only published studies with full-text articles were included.

Inclusion and Exclusion Criteria

The studies included in this meta-analysis had to meet the following criteria: (1) any study published as a case-control or cohort study that evaluated the association between IL-10 -1082A>G (rs1800896) polymorphism and breast cancer risk; (2) the numbers of cases and controls for each genotype were reported or sufficient data was provided to calculate the odds ratio (OR). The following were exclusion criteria: (1) not designed as case-control or cohort studies, (2) reviews, abstracts or animal studies; (3) studies were not relevant to IL-10 -1082A>G (rs1800896) polymorphism and breast cancer; (4) not providing the genotype frequencies; and (5) duplicate of previous publication. If multiple studies from the same case series were available, the one including the most individuals was used in the analysis.

Data Extraction

The information was carefully extracted from all of the eligible studies independently by two investigators based on the inclusion criteria listed above and then examined by an expert in headaches. From each of the included articles the following data were collected: first author, year of publication, country of origin, ethnicity, total number of cases and controls, frequencies of genotypes, genotyping technique, minor allele frequencies (MAFs), P-value for Hardy-Weinberg equilibrium (HWE). In case of disagreement, consensus was obtained on every item by joint review of the study. The different ethnic descents were categorized as Asian, European, American or African.

Statistical Methods

The odds ratio (OR) and its 95% confidence interval (CI) was used to assess the strength of association between IL-10 -1082A>G (rs1800896) polymorphism and breast cancer risk under allele model (G vs. A), homozygote model (GG vs. AA), heterozygote model (GA vs. AA), dominant model (GG+GA vs. AA), and
recessive model (GG vs. GA+AA). The significance of the pooled OR was determined by the Z-test. Heterogeneity assumption was checked by the Chi-square-based Q-test. The effect of heterogeneity was quantified using the I^2 value as well as P value. A P-value less than 0.10 for the Q-test and I^2 value >50% indicates existence of heterogeneity among studies. The pooled OR was assessed in both fixed-effects model (the Mantel–Haenszel method) and random-effects model (the DerSimonian and Laird methods), so the pooled OR estimates of the included studies was calculated by the random-effects model. Otherwise, the fixed-effects model was used. Sensitivity analyses were performed to evaluate the stability of the results, namely, a single study in the meta-analysis was omitted in each turn to reflect the influence of the single data set on the pooled results. Deviation from the Hardy–Weinberg equilibrium (HWE) was checked among controls through exact test. Subgroup analyses by ethnicity and studies quality were performed subsequently. Begg’s funnel plot was carried out to examine the potential publication bias between studies (P value less than 0.10 was selected to be statistically significant). In addition, Egger’s test on the natural logarithm scale of the OR was used to estimate the funnel plots asymmetry. All statistical analyses were performed using Comprehensive Meta-Analysis (CMA) software version 2.0 (Biostat, USA). All P values were two-sided, and P<0.05 was considered statistically significant.

RESULTS

Characteristics of Selected Studies

We have identified 211 published case-control studies before September 20, 2017 in the database search and by manual screening. Of these studies, the first screening excluded 109 publications that were excluded as duplicates or not relevant, leaving 102 studies for further selection. After removal of review articles, case reports, and those that did not meet our inclusion criteria, a total of 17 articles with 3,275 cases and 3,416 controls were finally included in our meta-analysis. A flow diagram schematizing the inclusion and exclusion process of identified articles with the inclusion criteria is pre-
sented in Figure 1. These studies were published between 2003 and 2017 and the average sample size was 192 cases per study. Of the 17 case-control studies focusing on the relationship between IL-10 -1082A>G (rs1800896) polymorphism and breast cancer, seven were conducted among Caucasians, with 1336 cases and 1388 controls, eight among Asians, with 1,754 cases and 1,898 controls, and two among Africans, with 185 cases and 130 controls. The studies were carried out in Italy, UK, USA, Canada, Turkey, Iran, China, India, Jordan and Egypt. The detailed characteristics of the included studies were shown in Table 1. The distribution of the genotypes in the control group of five case-control studies was not in agreement with Hardy-Weinberg equilibrium (HWE). Twelve of 17 studies were in accordance with HWE were defined as high-quality studies. The genotypes distributions in the individual studies were presented in Table 1.

### Quantitative synthesis

The main characteristics of these studies were listed in Table 2. The heterogeneity between studies was significant under all genetic models. Therefore, the random effect model was used for calculating the pooled OR. Overall, there was no significant associ-

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### TABLE 1. MAIN CHARACTERISTICS OF STUDIES INCLUDED IN THIS META-ANALYSIS.

<table>
<thead>
<tr>
<th>First Author/Year</th>
<th>Country/Ethnicity</th>
<th>Case Control Cases</th>
<th>Genotype</th>
<th>Allele</th>
<th>Controls Genotype</th>
<th>Allele</th>
<th>MAFs</th>
<th>HWE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giordani 2003</td>
<td>Italy (Caucasian)</td>
<td>125 100 60 54 11 174 76</td>
<td>AA AG GG A G</td>
<td>0.415</td>
<td>0.614</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smith 2004</td>
<td>UK (Caucasian)</td>
<td>144 263 32 58 39 136 122</td>
<td>AA AG GG A G</td>
<td>0.524</td>
<td>0.238</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guzowski 2005</td>
<td>USA (Caucasian)</td>
<td>50 25 10 28 12 48 52</td>
<td>AA AG GG A G</td>
<td>0.400</td>
<td>1.000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdolrahim-Zadeh 2005</td>
<td>Iran (Asian)</td>
<td>275 320 119 116 40 177 373</td>
<td>AA AG GG A G</td>
<td>0.348</td>
<td>0.012</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balasu-bramanian 2006</td>
<td>UK (Caucasian)</td>
<td>497 498 121 253 123 499 495</td>
<td>AA AG GG A G</td>
<td>0.504</td>
<td>0.323</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onay 2006</td>
<td>Canada (Caucasian)</td>
<td>398 372 90 205 103 385 411</td>
<td>AA AG GG A G</td>
<td>0.451</td>
<td>0.307</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scola 2006</td>
<td>Italy (Caucasian)</td>
<td>84 106 28 40 16 96 72</td>
<td>AA AG GG A G</td>
<td>0.410</td>
<td>0.206</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gonullu 2007</td>
<td>Turkey (Caucasian)</td>
<td>38 24 13 22 3 48 28</td>
<td>AA AG GG A G</td>
<td>0.187</td>
<td>0.834</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kong 2010</td>
<td>China (Asian)</td>
<td>315 322 285 29 1 599 31</td>
<td>AA AG GG A G</td>
<td>0.060</td>
<td>0.422</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooja 2012</td>
<td>India (Asian)</td>
<td>200 200 132 60 8 324 76</td>
<td>AA AG GG A G</td>
<td>0.150</td>
<td>0.781</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liang 2013</td>
<td>China (Asian)</td>
<td>40 89 31 9 0 71 9</td>
<td>AA AG GG A G</td>
<td>0.089</td>
<td>0.351</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vinod 2015</td>
<td>India (Asian)</td>
<td>125 160 76 31 18 183 67</td>
<td>AA AG GG A G</td>
<td>0.337</td>
<td>0.254</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alsuhaibani 2016</td>
<td>Egypt (African)</td>
<td>80 80 16 47 17 79 81</td>
<td>AA AG GG A G</td>
<td>0.512</td>
<td>0.024</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atoum 2016</td>
<td>Jordan (Asian)</td>
<td>202 210 157 29 16 343 61</td>
<td>AA AG GG A G</td>
<td>0.181</td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tian 2017</td>
<td>China (Asian)</td>
<td>312 312 51 132 129 234 390</td>
<td>AA AG GG A G</td>
<td>0.666</td>
<td>0.050</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maruthi 2017</td>
<td>India (Asian)</td>
<td>285 285 80 146 59 262 308</td>
<td>AA AG GG A G</td>
<td>0.408</td>
<td>0.009</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sabet 2017</td>
<td>Egypt (African)</td>
<td>105 50 15 41 49 71 139</td>
<td>AA AG GG A G</td>
<td>0.250</td>
<td>0.396</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MAFs: minor allele frequencies; HWE: Hardy–Weinberg equilibrium
FIGURE 2. FOREST PLOT OF IL-10 -1082A>G POLYMORPHISM AND BREAST CANCER RISK. A: OVERALL (RECESSIVE MODEL: GG VS. GA+AA); B: ASIANS (DOMINANT MODEL: GG+GA VS. AA), C: HWE STATUS (ALLELE MODEL: G VS. A).
Association between the IL-10 -1082A>G (rs1800896) polymorphism and breast cancer risk under the allele model (G vs. A: OR = 1.184, 95% CI = 0.895-1.180, p = 0.230), homozygote model (GG vs. AA: OR = 1.430, 95% CI = 0.927-2.204, p = 0.106), heterozygote model (GA vs. AA: OR = 0.966, 95% CI = 0.765-1.221, p = 0.774), dominant model (GG+GA vs. AA: OR = 0.957, 95% CI = 0.697-1.314, p = 0.786), and recessive model (GG vs. GA+AA: OR = 1.221, 95% CI = 0.981-1.518, p = 0.073, Figure 2A).

We have also carried out subgroup analyses that were stratified by ethnicity. Overall, no obvious evidence of associations between the IL-10 -1082A>G (rs1800896) polymorphism and susceptibility to the breast cancer were found in Caucasian, Asian and African populations under all genetic models (Figure 2B). Moreover, subgroup analysis of studies with high quality (HWE status) did not show significant association between IL-10 -1082A>G (rs1800896) polymorphism and increased risk of breast cancer (Figure 2C). The results of these analyses are shown in Table 2 and Figure 2.

Sensitivity Analysis

Sensitivity analysis was performed to confirm the stability and liability of the meta-analysis by sequentially omitting individual eligible studies. When any single study was excluded, the corresponding ORs were not materially changed (data was not shown), indicating the stability of our results. Additionally, we excluded the studies that genotype distribution in the controls deviating from HWE, and the corresponding pooled ORs were not significantly changed.

Publication Bias

Table 2 and Figure 3 present information related to the publication bias. We have performed Funnel plot and Egger’s linear regression to assess the publication bias of the included studies. The shapes of the funnel plots did not reveal any evidence of obvious asymmetry (Figure 3). In addition, the results of Begg’s test also showed that there was no strong statistical evidence of publication bias.
TABLE 2. RESULTS OF META-ANALYSIS FOR RS1800896 (-1082A>G) POLYMORPHISM AND RISK OF BREAST CANCER.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Genetic model</th>
<th>Type of model</th>
<th>Heterogeneity</th>
<th>Odds ratio</th>
<th>Publication Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>I2%</td>
<td>PH</td>
<td>OR</td>
</tr>
<tr>
<td>Overall</td>
<td>G vs. A</td>
<td>Random</td>
<td>91.84</td>
<td>&lt;0.001</td>
<td>1.184</td>
</tr>
<tr>
<td></td>
<td>GG vs. AA</td>
<td>Random</td>
<td>80.82</td>
<td>&lt;0.001</td>
<td>1.430</td>
</tr>
<tr>
<td></td>
<td>GA vs. AA</td>
<td>Random</td>
<td>69.43</td>
<td>&lt;0.001</td>
<td>0.966</td>
</tr>
<tr>
<td></td>
<td>GG+GA vs. AA</td>
<td>Random</td>
<td>84.38</td>
<td>&lt;0.001</td>
<td>0.957</td>
</tr>
<tr>
<td></td>
<td>GG vs. GA+AA</td>
<td>Fixed</td>
<td>49.63</td>
<td>0.013</td>
<td>1.221</td>
</tr>
</tbody>
</table>

By Ethnicity

Caucasian

| G vs. A       | Random        | 77.38| <0.001 | 1.018| 0.781-1.327 | 0.135 | 0.893 | 0.367 | 0.796 |
| GG vs. AA     | Random        | 83.43| <0.001 | 1.574| 0.779-3.183 | 1.264 | 0.206 | 1.000 | 0.715 |
| GA vs. AA     | Random        | 59.18| 0.023 | 1.067| 0.769-1.481 | 0.391 | 0.696 | 0.548 | 0.413 |
| GG+GA vs. AA  | Random        | 88.89| <0.001 | 0.876| 0.458-1.675 | -0.400 | 0.689 | 0.367 | 0.935 |
| GG vs. GA+AA  | Fixed         | 22.75| 0.256 | 1.159| 0.963-1.394 | 1.786 | 0.073 | 0.921 | 0.990 |

Asian

| G vs. A       | Random        | 94.51| <0.001 | 1.100| 0.670-1.805 | 0.377 | 0.706 | 0.173 | 0.683 |
| GG vs. AA     | Fixed         | 50.38| 0.060 | 1.005| 0.784-1.286 | 0.036 | 0.972 | 1.000 | 0.985 |
| GA vs. AA     | Random        | 72.47| 0.014 | 0.803| 0.578-1.116 | -1.308 | 0.191 | 0.107 | 0.408 |
| GG+GA vs. AA  | Random        | 68.18| 0.003 | 0.857| 0.643-1.143 | -1.050 | 0.294 | 0.536 | 0.489 |
| GG vs. GA+AA  | Fixed         | 14.56| 0.319 | 1.146| 0.937-1.403 | 1.326 | 0.185 | 0.763 | 0.854 |

African

| G vs. A       | Random        | 96.13| <0.001 | 2.377| 0.409-13.808 | 0.965 | 0.355 | NA    | NA    |
| GG vs. AA     | Random        | 94.09| <0.001 | 6.104| 0.139-267.71 | 0.938 | 0.348 | NA    | NA    |
| GA vs. AA     | Random        | 83.36| 0.014 | 1.700| 0.410-7.055 | 0.731 | 0.465 | NA    | NA    |
| GG+GA vs. AA  | Random        | 92.78| <0.001 | 2.448| 0.308-19.481 | 0.846 | 0.397 | NA    | NA    |
| GG vs. GA+AA  | Random        | 91.91| <0.001 | 4.446| 0.243-81.259 | 1.006 | 0.314 | NA    | NA    |

High Quality Studies

| G vs. A       | Random        | 85.14| <0.001 | 1.170| 0.887-1.542 | 1.112 | 0.266 | 0.303 | 0.397 |
| GG vs. AA     | Random        | 82.01| <0.001 | 1.842| 0.991-3.423 | 1.932 | 0.053 | 0.436 | 0.952 |
| GA vs. AA     | Random        | 73.26| <0.001 | 1.076| 0.785-1.474 | 0.455 | 0.649 | 0.537 | 0.335 |
| GG+GA vs. AA  | Random        | 88.06| <0.001 | 1.036| 0.649-1.654 | 0.150 | 0.881 | 0.303 | 0.648 |
| GG vs. GA+AA  | Random        | 58.11| 0.008 | 1.330| 0.948-1.866 | 1.648 | 0.099 | 0.876 | 0.433 |

Minor Allele Frequency

The present data revealed variation in the minor allele frequency of the IL-10 -1082A>G polymorphism worldwide (Table 1). The minor allele frequency range was from 18.7% (Turkey) to 52.4% (UK) among Caucasians, 6% (China) to 66.6% (China) among Asians, 25% to 51.2% among Africans (Egypt).

Discussion

Previous meta-analysis by Dai et al., demonstrated that IL-10 -1082A>G polymorphism did not significantly associate with breast cancer risk. They have included only nine case-control studies with 1851 cases and 1910 controls on IL-10 -1082A>G polymorphism association. To further explore and examine the association of IL-10 -1082A>G polymorphism with breast cancer, we conducted this meta-analysis only with most recently published studies on different populations. Compared with the previous meta-analyses, in this meta-analysis we have focused only on association between -10 -1082A>G polymorphism and breast cancer using 17 case-controls studies with 3275 cases and 3416 controls. However, Dai et al. study essentially remain an open field, as meta-analysis of their results' reliability and the number of studies were considerably smaller than that needed to reach robust conclusions. Moreover, they have not included the Abdolrahim-Zadeh et al. study that was published in 2005 in Iran. Also, in the current meta-analysis, we have carried out subgroup analysis by ethnicity among African population. Overall, our results were consistent with Dai et al. results and did not show a significant relationship between IL-10 -1082A>G...
polymorphism and breast cancer. In the subgroup analysis by ethnicity, there was also no association between IL-10 -1082A>G polymorphism and breast cancer risk in Caucasians, Asians and Africans.

Between-study heterogeneity is a common problem in meta-analysis for genetic association studies. In the current meta-analysis, there was a significant heterogeneity in association of IL-10 -1082A>G (rs1800896) polymorphism under all genetic models. A number of characteristics that vary among studies could be the sources of heterogeneity such as age, gender, ethnicity, sample size, including criteria, source of controls, and genotyping method. Therefore, we used meta-regression by ethnicity, which aim to reduce heterogeneity; however, we did not find any meaningful reduction in stratified analysis by ethnic and high quality studies, both of which were considered to be the relevant factors of Heterogeneity.

The main strengths of the current meta-analysis were obtaining more precise estimates, absence of publication bias, pooled data from studies from different ethnicities and sensitivity analysis indicated that our results were statistically robust. Despite these advantages, our meta-analysis also has some limitations which should be acknowledged when interpreting the results. First, the sample size was relatively small, and all data were from case-control studies. Second, we have included only studies that were published in English and Chinese languages and available full-text papers in the current meta-analysis; therefore, some eligible studies that have not been unpublished or were reported in other languages were missed, which may bias the power of our results. Third, the current meta-analysis results were based on single-factor estimates without adjustment for other risk factors such as age, gender, folate status, and specific environmental or lifestyle factors, should be conducted if possible. Finally, gene-gene, gene-environment or even the different polymorphisms of the IL-10 gene interactions were not estimated in this meta-analysis due lacking of the sufficient data.

In conclusion, our meta-analysis suggests that IL-10 -1082A>G (rs1800896) polymorphism not associated with an increased risk of breast cancer. Nevertheless, more studies are warranted to confirm the results and to establish the underlying molecular mechanisms that are involved.

REFERENCES


