Lack of association between the aryl hydrocarbon receptor rs2066853 polymorphism and breast cancer: A meta-analysis on Ahr polymorphism and breast cancer

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ABSTRACT. Published data regarding the association between aryl hydrocarbon receptor (Ahr) rs2066853 polymorphism and the risk of breast cancer shows conflicting results. We performed a meta-analysis on 2999 patients and 3050 controls from three related case-control studies to estimate the association between Ahr rs2066853 polymorphism and the risk of breast cancer. The protocol was approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Florida (America NIH Publication No. 86-231985 Revision). According to the three eligible populations, the odds ratios (ORs), 95% confidence intervals (CIs) on the risk of breast cancer for the genotypes GA vs GG, AA vs GG, and A vs G
were 1.06 (0.81-1.40), 0.96 (0.81-1.13), and 1.02 (0.85-1.22), respectively. The OR (95%CI) for GA + AA vs GG was 1.05 (0.80-1.37). Furthermore, after multi-variates adjustment, the ORs (95%CIs) were 1.05 (0.80-1.38) for GA vs GG, and 0.92 (0.76-1.10) for AA vs GG. This meta-analysis suggests that Ahr (rs2066853) polymorphism would not modify the risk of breast cancer. However, further research should be conducted to provide more evidence.

Key words: Ahr; Gene; Polymorphism; Breast cancer; Meta-analysis

INTRODUCTION

The aryl hydrocarbon receptor (Ahr) is a member of the basic helix-loop-helix/PER-AHR nuclear translocator (ARNT)-SIM superfamily of nuclear receptors (Tan et al., 2010). It regulates a wide range of developmental and toxicological processes including cell proliferation and xenobiotic metabolism (Meyer and Perdew, 1997; Marlowe and Puga, 2005; Kawajiri and Fuji-Kuriyama, 2007). In addition, it is regarded to play a contributory role in cancer (Nebert et al., 2004; Bradshaw et al., 2008).

Ahr is a key regulator of transcriptional expression for cytochrome P450 (Sangrajrang et al., 2009). Ahr rs2066853 (Arg554Lys) is located in exon 10, a region that encompasses a major portion of the trans-activation domain of this gene (Long et al., 2006). Some studies have explored the relationship between Ahr and the risk of cancers, including lung cancer (Kawajiri et al., 1995; Cauchi et al., 2001) and bladder cancer (Zhang et al., 2002). Furthermore, previous research has also been conducted to determine the relationship between Ahr rs2066853 polymorphism and the risk of breast cancer. However, the results of these studies were inconclusive. Therefore, we conducted a meta-analysis on all eligible case-control studies to estimate the association between Ahr (rs2066853) polymorphism and the risk of breast cancer.

MATERIAL AND METHODS

Search strategy

Literature searches were conducted using the databases PubMed, EMBASE, and the COCHRANE Library, which were in English. In addition, the Chinese databases VIP, CNKI, and Sinomed (up to Sep. 18, 2014) were also used. The following keywords and subject terms were included: 'Ahr' or 'aryl hydrocarbon receptor gene' and 'breast cancer'. References of received articles were also further investigated.

Inclusion criteria

Studies included in this meta-analysis required the following criteria: (a) being a case-control study, (b) individual studies involved only unrelated study participants, and (c) the relationship between the Ahr polymorphism and breast cancer was evaluated.

Exclusion criteria

Case reports, review articles, editorials, clinical guidelines, and information articles for pa-
patients were all excluded. Individual studies in which information regarding Ahr polymorphism were insufficiently described were also rejected.

Data extraction

Literature research was independently conducted by two investigators (Y.L. and H.Z.Q.), and the studies were then screened for inclusion and appraisal. Discrepancies were adjudicated by third party persons who were familiar with the related studies. Agreements were reached following discussions. Data were collected from each publication including the authors, year of publication, country, ethnicity, journal, study design, sample size, resources of controls, and information regarding Ahr polymorphism. The Newcastle-Ottawa-Scale (NOS) was used to quantify study quality (Cota et al., 2013).

Statistical analysis

Unadjusted odds ratio (OR) with corresponding 95% confidence interval (CI) of each selected study was first calculated. The pooled OR was examined using the Z-test. Heterogeneity among studies was measured by the Q-statistic test and I-square statistic test. Both fixed-models using the Mantel-Haenszel method and random-effect models were included in this meta-analysis.

Hardy-Weinberg (H-W) equilibrium was assessed using Pearson Chi-square test for the controls in each study.

Potential publication bias was accessed by Funnel plot and Egger’s linear regression. All analyses were performed by the software Stata, version 8.0 (Stata Corp, College Station, TX, USA). The tests were two-sided. Statistical significance was defined as P < 0.05.

RESULTS

Study characteristics and meta-analysis database

A total of nine potential papers were found according to our search terms from the databases PubMed, EMBASE, and the COCHRANE Library (restricted to human research). No related paper in Chinese was found. Among the nine papers, three of those focused on the function of Ahr in breast cancer cells (Abdelrahim et al., 2003; Zhao et al., 2012; Tarnow et al., 2013). One study was based on a cohort study among patients (Long et al., 2007). Two studies did not show sufficient information on Ahr (rs2066853) polymorphism (Georgitsi et al., 2007; Tan et al., 2010). Therefore, a total of three individual studies (Le Marchand et al., 2005; Long et al., 2006; Sangrajrang et al., 2009) were included in this meta-analysis. Data from 2999 patients and 3050 controls were obtained from the included. Breast cancer in patients was confirmed by clinical as well as other assistant examinations.

A dataset based on the extracted information from each included report was established (Table 1). Quality assessment for the eligible studies according to the NOS is shown in Table 2.

Quantitative synthesis

The average relative frequencies of the A allele, AA genotype, and GA genotype from the three populations were 31.85, 10.76, and 40.65% in breast cancer patients and 31.29, 10.98, and 38.31% in the controls, respectively. The genotype distributions of Ahr (rs2066853) in controls from only the first and second eligible study populations satisfied the H-W equilibrium (P > 0.05).
Table 1. Characteristics of literatures included in this analysis.

<table>
<thead>
<tr>
<th>ID</th>
<th>First author</th>
<th>Year</th>
<th>Country</th>
<th>Ethnicity</th>
<th>Source of controls</th>
<th>Genotyping method</th>
<th>Sample size (case/control)</th>
<th>Polymorphisms distribution of Ahr rs2068853 (case/control)</th>
<th>Allele distribution of Ahr rs2068853 (case/control)</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sangrajrang S</td>
<td>2009</td>
<td>Thailand</td>
<td>Asian</td>
<td>HB</td>
<td>TaqMan</td>
<td>570/497</td>
<td>236/245 260/189 594/48</td>
<td>736/679 378/285</td>
<td>1.34 (1.02, 1.76) 1.23 (0.79, 1.92)</td>
</tr>
<tr>
<td>2</td>
<td>Long JR</td>
<td>2006</td>
<td>China</td>
<td>Asian</td>
<td>PB</td>
<td>High-throughput sequencing</td>
<td>1090/1183</td>
<td>472/444 455/516 113/139</td>
<td>1399/1404 681/794</td>
<td>0.82 (0.69, 0.99) 0.76 (0.58, 1.01)</td>
</tr>
<tr>
<td>3</td>
<td>Marchand LL</td>
<td>2005</td>
<td>UAS</td>
<td>Mixed</td>
<td>PB</td>
<td>PCR/RFLP</td>
<td>1339/1370</td>
<td>721/756 463/456 155/158</td>
<td>1905/1968 773/772</td>
<td>1.1 (0.9, 1.3) 1.0 (0.7, 1.3)</td>
</tr>
</tbody>
</table>

ID: study id; HB: hospital based; PB: population based.
Table 2. Quality assessment for eligible studies according to NOS.

<table>
<thead>
<tr>
<th>ID</th>
<th>First author</th>
<th>Selection</th>
<th>Comparability</th>
<th>Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sangrajrang S</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>Long JR</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>Marchand LL</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

The NOS for case-control study: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. Therefore, a maximum of four stars can be given for Selection, three stars for Outcome. A maximum of two stars can be given for Comparability. More stars mean higher quality of the eligible studies. a: means the number of stars.

Compared with the GG genotype, no statistically significant relationship was found between GA, AA and the risk of breast cancer. The odds ratios (ORs), 95% confidence intervals (CIs), and the P heterogeneity values for GA and AA on the risk of breast cancer were 1.06 (0.81, 1.40), 0.003, 0.96 (0.81, 1.13), and 0.106, respectively. At the same time, the A allele also did not significantly increase the risk of breast cancer, as compared with the G allele. The corresponding OR (95%CI) was 1.02 (0.85, 1.22), P heterogeneity = 0.006. Compared with the GG genotype, GA+ AA genotypes also did not modify the risk of breast cancer with OR (95%CI) and P heterogeneity value of 1.05 (0.80, 1.37) and 0.002, respectively.

Following multi-variates adjustment, GA, AA genotypes still did not modify the risk of breast cancer as compared with the GG genotype. The corresponding ORs (95%CIs) and P heterogeneity values were 1.05 (0.80, 1.38) and 0.006 for GA vs GG. ORs (95%CIs) and P heterogeneity for AA vs GG were 0.92 (0.76, 1.10) and 0.154, respectively.

Publication bias

Funnel plots and Egger’s tests were conducted to examine publication bias (Figure 1). No publication bias was found for GA vs GG, P = 0.602.

![Figure 1](image_url). Association of Breast cancer with the Ahr rs2066853 genotype by random model (GA vs GG) plotted as an OR Forest plots with 95%CI Heterogeneity = 11.46 p = 0.003, I^2 = 82.6%, z = 0.44 P = 0.659. Black square indicates the value of OR; size of the square is inversely proportional to its variance. Horizontal line denotes 95% confidence interval (CI) of OR; black diamond indicates pooled results; studies were ordered by published year.
A meta-analysis on Ahr polymorphism and breast cancer

DISCUSSION

The present meta-analysis consisting of data compiled from three related case-control studies explored the relationship between Ahr (rs2066853) polymorphism and the risk of breast cancer. We did not observe any significant increase in breast cancer development in A (rs2066853) allele carriers. Furthermore, no statistically significant relationship was found following multi-variate adjustments. Heterogeneity among eligible studies was found, and therefore, random-effect models were used in this analysis. No evidence of publication bias was found in this meta-analysis, and all three studies received high quality score according to the NOS.

Ahr is found in multiple human organs, and is highly expressed in different kinds of cancers (Vezina et al., 2009; Liu et al., 2013; Wang et al., 2013). Sangrajrang et al (2009) found that among the women in Thailand, GA heterozygotes of Ahr (rs2066853) increased the risk of breast cancer, while in Chinese women, this polymorph showed the contrary influence on the risk of breast cancer (Sangrajrang et al., 2006). However, neither of such findings was replicated in other studies including those included in this meta-analysis. Pooled analysis based on the multi-variate adjustment ORs (95%CIs) did not find any statistically significant relationship between GA/AA (rs2066853) genotypes and the risk of breast cancer. Therefore, our meta-analysis suggests that the A allele on the Ahr gene does not modify the risk of breast cancer.

Some limitations in our meta-analysis should be considered when interpreting the results. Since only three studies were included in this meta-analysis with low between-study, sensitivity analysis was not performed. In addition, language limitation may have hindered information interpretation. Furthermore, lacking the original data of the reviewed studies, evaluation of results was limited. It is possible that other factors such as gene-gene, gene-environment, and even different polymorphic loci of the same gene may modulate breast cancer risk. In spite of these limitations, our meta-analysis also included several advantages. First, a large number of cases and controls were pooled, which significantly increased the statistical power of the analysis. Secondly, the quality of all case-control studies included in the current meta-analysis was considered satisfactory, and met our inclusion criterion.

In conclusion, this meta-analysis suggested that A allele of Ahr (rs2066853) did not significantly modify the risk of breast cancer. However, because of the comparatively insufficient published studies included, we were not able to systematically analyze the relationship between Ahr (rs2066853) and the risk of breast cancer. More evidence from epidemiologic researches is needed to provide a more clear characterization of the role of Ahr (rs2066853), and whether it exerts any influence on genetic susceptibility to breast cancer development.

Conflicts of interest

The authors declare no conflict of interest.

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Y. Li and H.Z. Qin searched the materials independently. Y. Li analyzed the data involved in this meta-analysis, and explained the results. H. Qin, Q. Song, X.D. Wu, and J.H. Zhu checked the materials, and explained the results. J.H. Zhu supported the research.
REFERENCES


