Association between Pax8-PPARγ1 Rearrangement and Follicular Thyroid Cancer: a Meta-Analysis

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Abstract

Background: Pax8 and peroxisome proliferator-activated receptor gamma 1 gene (Pax8-PPARγ1) are important factors in tumors. Several studies have suggested that follicular thyroid cancer may arise from Pax8-PPARγ1 rearrangement. In order to have a better understanding of the association between Pax8-PPARγ1 rearrangement and follicular thyroid cancer, we conducted the present meta-analysis.

Materials and Methods: The information was extracted from PubMed, EMBASE and Web of Science. Odds ratios (ORs) were calculated using a fixed-effects model. We also performed heterogeneity and publication bias analyses. Results: Nine studies including 198 follicular thyroid cancer patients and 268 controls were considered eligible. The frequency of Pax8-PPARγ1 rearrangement was significantly higher in the follicular thyroid cancer group than in the control group, with a pooled OR of 6.63 (95% CI=3.50-12.7). In addition, through subgroup analysis, the OR between Pax8-PPARγ1 rearrangement and follicular thyroid cancer was 6.04 (95% CI = 3.18-11.5) when using benign tumor tissues as controls. The OR for the method subgroup was 9.99 (95% CI =4.86-20.5) in the RT-PCR. Conclusions: The final results demonstrated that Pax8-PPARγ1 rearrangement has significant association with follicular thyroid cancer.

Keywords: Follicular thyroid cancer - Pax8-PPARγ1 rearrangement - meta-analysis
letters or irrelevant studies, therefore read the full text of 11 papers and 9 of them met the standards of NOS (Newcastle-Ottawa Scale), which involved 198 cases and 268 controls in the meta-analysis (Kroll et al., 2000; Marques et al., 2002; Nikiforova et al., 2002; Dwight et al., 2003; Lacroix et al., 2004; Lacroix et al., 2005; Castro et al., 2006; Banito et al., 2007; Boos et al., 2013). Figure 1 provided the details of selecting process [Figure 1]. Basic information of the eligible studies is shown in Table 1.

Quality Assessment and Data Extraction
Three investigators independently selected studies and extracted data (Hangyu Li, Zhihao Xie, and Conghui Xu). According to the Cochrane Handbook for systematic reviews, information about first author’s name, year of publication, control type, the number of individuals in the case and control groups, the measuring methods of the Pax8-PPARγ1 rearrangements, and frequencies of the Pax8-PPARγ1 rearrangements in the case and control groups had been reconfirmed by two reviewers (Hangyu Li and Zhihao Xie). We chose to use Newcastle-Ottawa Scale (NOS) to assess the quality of the studies marked 9-star (range: 0 to 9) to each research.

Methods of Statistical Analysis
Review Manager 5.1 (RevMan 5.1, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and Stata software version 12.0 (StataCorp., College Station, TX, USA) were used for Meta-Analysis and we chose pooled odds ratios (ORs) with 95% confidence intervals (CIs) to describe the association between Pax8-PPARγ1 rearrangements and follicular thyroid cancer. Heterogeneity among studies was evaluated by the Cochran Q test and the I parameter. And p<0.05 or I²>50% was considered as significant heterogeneity. To calculate the pooled ORs, the Mantel–Haenszel method was used. Besides, subgroup analysis was applied to explore the heterogeneity. Significant publication bias are main drawbacks in Meta-Analysis, so we assessed publication bias with a funnel plot (Stang, 2010), Egger’s test (Begg and Mazumdar, 1994) and the Peters test (Peters et al., 2006).

Results

Quality Assessment and Selected studies
NOS was applied to evaluate the quality of the studies and 2 studies were eliminated because their scores are less than 5-stars. Finally, we included 9 studies in our Meta-Analysis. 7 studies [2, 4, 12, 13, 14, 15, 16] used reverse transcription–polymerase chain reaction (RT-PCR), and 2 studies [17, 18] used fluorescence in situ hybridization (FISH) to explore the expression of Pax8-PPARγ1 in cases and control. Table 1 shows the basic information of the 9 studies

<p>| Table 1. Basic Information of the 9 Studies |</p>
<table>
<thead>
<tr>
<th>Author</th>
<th>Publication year</th>
<th>Pax8-PPAR+ total</th>
<th>Control type</th>
<th>Method</th>
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<tbody>
<tr>
<td>Kroll</td>
<td>2000</td>
<td>5/8</td>
<td>FTA</td>
<td>RT-PCR</td>
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<tr>
<td>Marques</td>
<td>2002</td>
<td>5/9</td>
<td>FTA</td>
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<tr>
<td>Nikiforova</td>
<td>2002</td>
<td>8/15</td>
<td>FTA</td>
<td>RT-PCR</td>
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<td>Dwight</td>
<td>2003</td>
<td>4/34</td>
<td>FTA</td>
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<td>Lacroix</td>
<td>2004</td>
<td>4/21</td>
<td>FTA</td>
<td>RT-PCR</td>
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<tr>
<td>Lacroix</td>
<td>2005</td>
<td>4/23</td>
<td>FTA</td>
<td>RT-PCR</td>
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<tr>
<td>Castro</td>
<td>2006</td>
<td>10/22</td>
<td>FTA</td>
<td>RT-PCR</td>
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<td>Banito</td>
<td>2007</td>
<td>7/17</td>
<td>FTA</td>
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</tr>
<tr>
<td>Boos</td>
<td>2013</td>
<td>6/49</td>
<td>FTA</td>
<td>RT-PCR</td>
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<tr>
<th>Table 2. Data of Subgroup Analysis</th>
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<tr>
<td>RT-PCR</td>
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<tr>
<td>FISH</td>
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</table>

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We identified 266 articles initially, of which 150 were left after removing duplicates. 124 studies were excluded by title, abstract and keywords review. 12 studies were excluded by full text review. 15 studies were excluded by full text review. 26 studies were evaluated by full text review. 9 studies were used in the meta-analysis.

Figure 1. Details of the Study Selection Process. This figure showed the process of studies screened. Finally, 9 studies had been chosen.

We performed subgroup analysis and tried to figure out the potential sources of heterogeneity. We assumed that heterogeneity may probably arise from the different method of evaluation (RT-PCR or other methods) and control type (benign tissues or normal tissues). Detailed information of subgroup analysis is listed in Table 2. Finally, the OR between Pax8-PPARγ1 rearrangements and follicular thyroid cancer was 6.01 (95% CI = 3.17–11.39) in benign thyroid tissues and 4.52 (95% CI = 0.81–25.12) in normal tissues under the fixed-effects model.

We used Begg’s funnel plot, Egger’s test and the Peters test to assess the publication bias of the literature. The symmetry of the plot suggests no publication bias. And no evidence of publication bias was detected by Peters test or Egger’s test (P = 0.382; Egger’s test, P = 0.564).

Discussion

Thyroid cancer is the most frequent endocrine cancer though it is less common among all human cancers (Pacini et al., 2006). Until now, the exact etiology of thyroid cancer is still unclear, but exposure to ionizing radiation is the best-known and only confirmed risk factor.

method of evaluation (RT-PCR or other methods) and control type (benign tissues or normal tissues). Detailed information of subgroup analysis is listed in Table 2. Finally, the OR between Pax8-PPARγ1 rearrangements and follicular thyroid cancer was 6.01 (95% CI = 3.17–11.39) in benign thyroid tissues and 4.52 (95% CI = 0.81–25.12) in normal tissues under the fixed-effects model.[Figure 3] And the OR for the method subgroup was 9.99 (95% CI = 4.86–20.51) in the RT-PCR and 1.43 (95% CI = 0.33–6.11) in the FISH group under the fixed-effects model.[Figure 4]

Our Meta-Analysis includes nine articles with 198
cases and 268 controls. Pax8-PPARγ1 rearrangements
level of the cases group was significantly higher than the
control group. The pooled odds ratio under fixed-effect
model was 6.63 (95% CI =3.50-12.56 ) in the cases group.
The study of subgroup showed us that the summary OR
was 6.01(95%CI=3.17-11.39) in benign thyroid tissue and
4.40(95%CI=0.79-24.49) in normal tissues, while the odds
ratio is 9.99 (95%CI=4.86-20.51) and 1.43(95%CI=0.33-
12.56) in RT-PCR and FISH test separately .

There were a number of limitations to the current
investigation. Firstly, we only included two variables in
subgroup analysis (control type and detection methods)
because of limited information and insufficiency of the
extracted data. Secondly, only published articles could
be searched from databases, Therefore possibilities are
that certain bias cannot be eliminated. If new studies are
published, we will continue to focus on their results.

Above all, Pax8-PPARγ1 rearrangements was proved
to have a significant association with follicular thyroid
cancer based on our Meta-Analysis. Accordingly, Pax8-
PPARγ1 rearrangements could be a biomarker in follicular
thyroid cancer diagnosis. Also, the association provides
a potential way to identify malignant or benign thyroid
tumor (FTC or FTA) through genetic test.

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