RESEARCH ARTICLE

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 presenmt meta-analysis. Materials and Methods: The information was extracted from PubMed, EMBASE and Web of Science. Statistic analysis was performed with Stata12.0 software. 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

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Introduction

We focused on a chromosomal translocation in t(2;3)(q13;p25), fusing Pax8-a transcription factor, which is the key of normal thyroid gland development, and the peroxisome proliferator-activated receptorγ(PPARγ), which is one of the thyroid cell nucleus receptor family (Eberhardt et al., 2010). Pax8-PPARγ1 oncogene was detected in thyroid carcinomas (78% of follicular carcinomas are FTC)(Marques et al., 2002). In addition, papillary thyroid carcinoma (PTC)may also harbor the Pax8-PPARγ1 fusion gene(Castro et al., 2005). Some studies even reported that the frequency of Pax8-PPARγ1 rearrangements was similar in FVPTC (37.5%), FTC45.5%)(Banito et al., 2007). Moreover, previous cytogenetic studies have identified the translocation in some cases of FTA(33.3%) (Dwight et al., 2003). But some studies reported that the frequency of Pax8-PPARγ1 rearrangements is 35% in FTC and 55% in FTA(Cheung et al., 2003). The main purpose of the meta-analysis is to identify if Pax8-PPARγ1 rearrangements lead to an increasing risk of FTC.

Materials and Methods

Search strategy and selection criteria

Based on the data extracted from PubMed, EMBASE, and Web of science, some potential relevant studies published up to March 20, 2015 were selected. The search strategy was the same for all the three databases, which was 'thyroid and (cancer or tumor or carcinoma) and Pax8-PPARγ1'. The selected studies must accord with the following criteria: 1) studies limited to human, 2) studies evaluated the association of Pax8-PPARγ1 rearrangements with follicular carcinomas, 3) studies either being a case-control one or one including case and control populations, 4) studies reporting the Pax8-PPARγ1rearrangements frequency in case and control groups. We extracted the main information from the title, key words and abstract and eliminated literature review, conference abstract,

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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). Figure1 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-PPARγ1rearrangements, and frequencies of the Pax8-PPARγ1rearrangements 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 $I^2>50\%$ 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 2studies [17, 18] used f 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[Table 1].

Heterogeneity and Data of Meta-Analysis

There is no significant heterogeneity among the 9

Table 1. Basic Information of the 9 Studies

Author	Publication year	Case		Control		Control type	Method
		Pax8-PPAR+	total	Pax8-PPAR+	total		
Kroll	2000	5	8	0	20	FTA	RT-PCR
				0	10	MH	RT-PCR
Marques	2002	5	9	2	16	FTA	RT-PCR
				0	2	MH	RT-PCR
Nikiforova	2002	8	15	2	25	FTA	RT-PCR
				0	16	HN	RT-PCR
Dwight	2003	4	34	1	40	FTA	RT-PCR
				0	2	NT	RT-PCR
Lacroix	2004	4	21	1	26	FTA	RT-PCR
				0	14	NT	RT-PCR
				0	13	HT	RT-PCR
Lacroix	2005	4	23	1	16	FTA	RT-PCR
				0	17	NT	RT-PCR
Castro	2006	10	22	3	9	FTA	FISH
Banito	2007	7	17	5	40	FTA	RT-PCR
Boos	2013	6	49	0	2	FTA	FISH

[1]FTA: Follicular thyroid adenoma; [2]MH: Multinodular hyperplasias; [3]HN: Hyperplastic nodules; [4]NT: Normal tissue; [5]HT: Hyperfunctioning tissues; [6]RT-PCR: Reverse transcription–polymerase chain reaction; [7]FISH: Fluorescence in-situ hybridization

Table 2. Data of Subgroup Analysis

Group	Case		Control		M-H pooled OR	Heterogeneity			Weight
	Pax8-PPAR(+)	Total	Pax8-PPAR(+)	Total	OR(95%CI)	X^2	P	I^2	
Total	53	198	15	268	6.63(3.50-12.56)	10.02	0.26	20%	100%
Control Type Subgroup									
BTT	53	198	15	235	6.04(3.18-11.45)	10.11	0.26	21%	83%
NT	12	78	0	33	4.52(0.81-25.12)	1.49	0.47	0%	17%
Method subgroup									
RT-PCR	37	127	12	257	9.99(4.86-20.51)	4.36	0.63	0%	61%
FISH	16	71	3	11	1.43(0.33-6.11)	0.2	0.66	0%	39%

[1]BTT: Benign thyroid tissue; [2]NT: Normal tissue; [3]M-H pooled OR: fixed-effect model

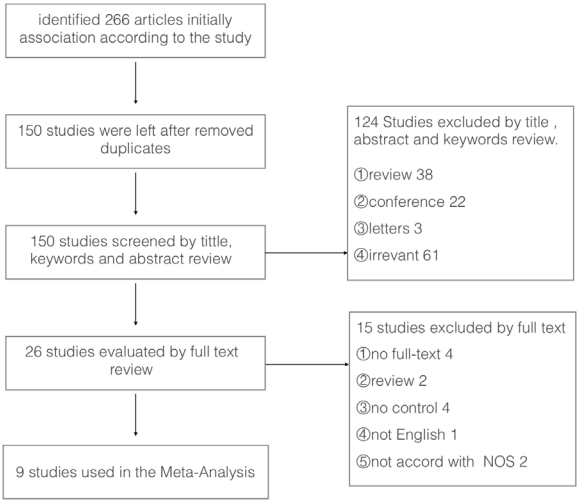

Figure 1. Details of the Study Selection Process. This figure showed the process of studies screened. Finally, 9 studies had been chosen

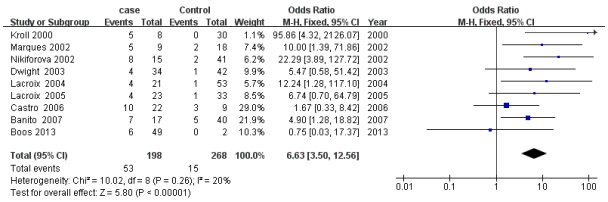

Figure 2. Results for Pax8-PPARγ1 Rearrangements Associated with Follicular Thyroid Cancer in the Meta-analysis. This figure showed OR for each study and the pooled OR between Pax8-PPARγ1 rearrangements and follicular thyroid cancer under the fixed-effects models

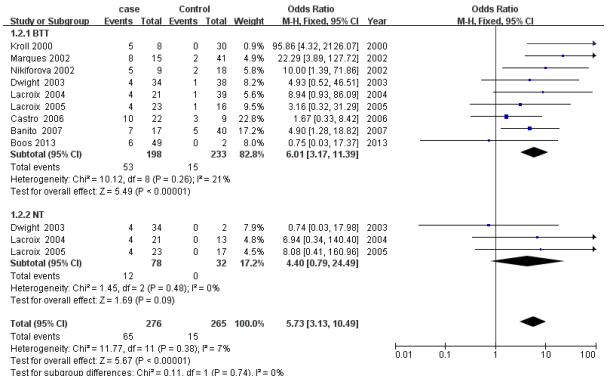

Figure 3. Subgroup Analysis of Different Control Types Adopted. This figure showed the forest plot for subgroup analysis among control type group

studies(I^2 = 20.0%, Q= 10.02, P=0.26). So we performed a fixed-effects model to estimate the association between Pax8-PPARγ1 rearrangements and follicular thyroid cancer. As a result, a significant association was found between Pax8-PPARγ1 rearrangements and follicular thyroid cancer, and the pooled odds ratio was 6.63 (95% CI = 3.50-12.56) [Figure 2].

Subgroup analysis

We processed subgroup analysis and tried to figure out the potential sources of heterogeneity. We assumed that heterogeneity may probably arise from the different

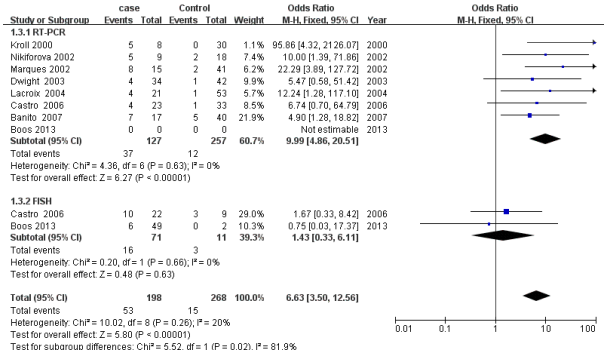

Figure 4. Subgroup Analysis of Different Methods Used by Studies. This figure showed the forest plot for subgroup analysis among method group

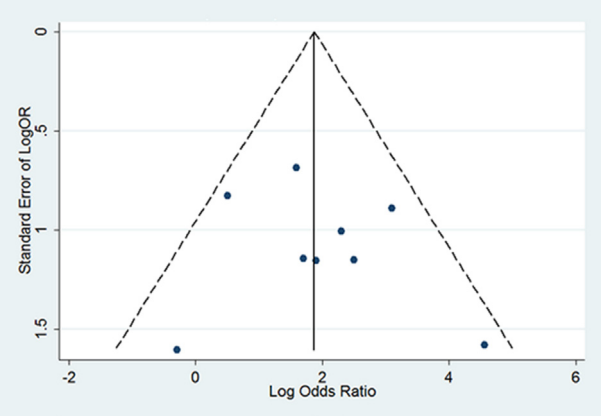

Figure 5. Begg's Funnel Plot for Publication Bias in the Meta-analysis. This figure showed publication bias through funnel plot. Each study was represented by an point and shape of the funnel plots showed symmetrical, suggesting no publication bias

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]

Publication Bias

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 Peter's test or Egger's test[Figure 5](Peter'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.

(Papadopoulou and Efthimiou, 2009). Very few studies have been conducted on the association between Pax8-PPARγ1rearrangements and FTC. Meta-analysis offered an opportunity for the combination of the information of Pax8-PPAR in the FTC and then provided possible summaries on their effect measures. This will help to further understand the association between Pax8-PPARγ1rearrangements and FTC and can also provide basis for future studies.

Our Meta-Analysis includes nine articles with 198 cases and 268 controls. Pax8-PPARγ1rearrangements 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.

Acknowledgements

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