Radiation exposure, young age, and female gender are associated with high prevalence of \textit{RET}/PTC1 and \textit{RET}/PTC3 in papillary thyroid cancer: a meta-analysis

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ABSTRACT

Background: \textit{RET}/PTC rearrangements have been identified as a specific genetic event in papillary thyroid cancer (PTC). We conducted this meta-analysis to identify an enriched population who were more likely to occur \textit{RET}/PTC fusion genes.

Methods: All relevant studies in the PubMed, Web of Science, and Embase databases were searched up to June 2015. The studies found were screened according to our inclusion and exclusion criteria. All analyses were performed using STATA software.

Results: Eventually, 38 eligible studies comprising 2395 participants were included. Overall analysis indicated that radiation exposure contributed to increased \textit{RET}/PTC risk (OR = 2.82; 95%CI: 1.38–5.78, \(P = 0.005\)). Stratified analysis according to \textit{RET}/PTC subtype and geographical area showed that this association was restricted to the \textit{RET}/PTC3 subtype (OR = 8.30, 95%CI: 4.32–15.96, \(P < 0.001\)) in the Western population. In addition, age < 18 years, i.e., young age, was associated with higher prevalence of \textit{RET}/PTC3 (OR = 2.03, 95%CI: 1.14–3.62, \(P = 0.017\)), especially in the radiation-exposure subpopulation (OR = 2.35, 95%CI: 1.01–5.49, \(P = 0.048\)). The association between female gender and \textit{RET}/PTC1 risk was more significant in the PTC patients without radiation exposure (OR = 1.69, 95%CI: 1.04–2.74, \(P = 0.034\)).

Conclusion: Both radiation exposure and young age are associated with increased risk of \textit{RET}/PTC3 and that female gender is associated with higher prevalence of \textit{RET}/PTC1 in the subpopulation without radiation exposure. The \textit{RET}/PTC status in combination with radiation exposure, age, and sex should be considered in the differential diagnosis of suspicious PTC.

INTRODUCTION

Rearrangement involving the \textit{RET} proto-oncogene, referred to \textit{RET}/PTC (the rearranged during transfection/papillary thyroid carcinoma tyrosine kinase) fusion genes, is one of the best-known mutations in papillary thyroid carcinoma (PTC) [1]. \textit{RET}/PTC is identified as a specific genetic event in patients with PTC, which forms the basis of differential diagnosis and novel therapeutic approaches to this disease [2]. However, the prevalence rate of the major \textit{RET}/PTC subtypes in different ethnicities and their correlation with the clinicopathologic features of PTC remains controversial and as yet are not routinely investigated in clinical practice.

The receptor tyrosine kinase \textit{RET} plays a critical role in cell differentiation and proliferation, which is required for normal development of several tissues, especially in early embryogenesis [3]. In 1985, Takahashi and colleagues initially reported \textit{RET} as a proto-oncogene that can be activated by interchromosomal rearrangement [4]. Subsequent studies demonstrated more than a dozen different forms of \textit{RET} rearrangement, of which \textit{RET}/PTC1 and \textit{RET}/PTC3 are the most common, resulting from the fusion of \textit{RET} with \textit{H4} and of \textit{RET} with \textit{RFG/ELE1}}
respectively [5]. However, their prevalence rates in PTC exhibit significant geographic variation, ranging from 0% to 86.7% among studies [6, 7]. As risk factors such as sex, age, and radiation exposure are related to PTC pathogenesis, scientists have focused on searching for the factors that increase RET/PTC rearrangement risk. Accordingly, several studies have detected RET/PTC rearrangements more frequently in PTC in children than in adults [8, 9]. A relatively high prevalence of RET/PTC rearrangements was reported in radiation-induced PTC [10]. In addition, ethnicity and demographic characteristics may also influence the frequency of RET/PTC rearrangement [11-13]. To date, numerous relevant studies have been published but with divergent results.

In this study, we aimed to identify an enriched population who were more likely to occur RET/PTC1 and RET/PTC3 fusion genes and to provide more useful information on candidate selection for PTC prevention, diagnosis, and treatment. Therefore, we performed this meta-analysis to investigate the association between the presence/absence of RET/PTC1 or RET/PTC3 and radiation exposure, sex, age, and ethnicity.

RESULTS

Basic characteristics of enrolled studies

The article selection flowchart is depicted in Figure 1. A total 2014 records were obtained by searching the PubMed, Web of Science, and Embase databases. After removing duplicates, we found 1206 potentially relevant records. By reviewing titles, abstracts, and full texts according to the inclusion and exclusion criteria, 1168 articles were excluded because they were not relevant, involved in vitro or animal experiments, were reviews or meeting abstracts, contained data covered by other studies, had no raw data, etc. Eventually, 38 full-text articles, which consisted of 2395 PTC cases, met our inclusion criteria and were included in the final meta-analysis [6-10, 14-47].

The main characteristics of the studies included in this meta-analysis are summarized in Table 1. The status of the RET/PTC fusion gene in the original studies were detected by PCR combined with reverse transcription (RT), Southern Blot or fluorescence in situ hybridization (FISH). The included studies involved populations from different geographical regions, namely Asia, Europe, and America; therefore, we divided the studies into Asian and Western subgroups.

We also summarized the positive rates of RET/PTC from each original study (Table 2). The overall prevalence of RET/PTC was relatively higher in the Western populations (42.19%) than in the Asian populations (36.73%). A similar tendency was observed for the RET/PTC1 subtype, whereas the Asian populations demonstrated a higher positive rate for the RET/PTC3 subtype (Asian vs. Western populations: 26.50% vs. 17.05%). In the Asian studies, the positive rates of RET/PTC3 in the studies by Lam et al. [16] and Rao et al. [7] were up to 85.71% and 86.67%, respectively, while another six studies reported a much lower incidence of RET/PTC3 that ranged from 0% to 20.79% [9, 14, 20-23].

Association between radiation exposure and RET/PTC fusion genes

As radiation exposure is the best-known risk factor for PTC, we initially investigated the effect of radiation on RET/PTC rearrangement (Table 3). Fourteen studies investigated the distribution difference of radiation exposure between RET/PTC-positive and -negative patients with PTC. When the RET/PTC1 and RET/PTC3 subtypes were combined, radiation exposure conferred increased overall risk for RET/PTC development (OR = 2.82, 95%CI: 1.38–5.78; P = 0.005, Figure 2) and there was moderate heterogeneity (I² = 74%, Phet < 0.001). Stratified analysis according to geographical region decreased the heterogeneity slightly, and increased risk for RET/PTC rearrangement persisted in the Western subpopulation, demonstrating an increased OR of 3.97 (95%CI: 2.03–7.75; P < 0.001).

When the RET/PTC1 and RET/PTC3 subtypes were considered separately, radiation exposure conferred significantly higher risk for RET/PTC3 rearrangement (OR = 8.30, 95%CI: 4.32–15.96; P < 0.001, Figure 3) but not for RET/PTC1 rearrangement. This association was only evident in the Western subpopulation. Separate pooled analysis for the RET/PTC1 and RET/PTC3 subtypes was not performed for the Asian subpopulation because three original studies involving this population investigated the combined status of RET/PTC1 and RET/PTC3, and the data could not be extracted separately [9, 15, 22]. Only one study with a small sample in an Asian country reported the RET/PTC1 and RET/PTC3 fusion gene data separately [21]. There was significant inter-study heterogeneity in the RET/PTC1 analysis but not in the RET/PTC3 analysis.

Association between RET/PTC fusion genes and age

Different age effects have been observed in the development of PTC, and we therefore explored whether young age affected the penetrance of the RET/PTC fusion genes in children and adolescents (Table 4). In this meta-analysis, age < 18 years was considered young, i.e., children and adolescents. In the combined analysis of the RET/PTC1 and RET/PTC3 subtypes, no association was observed between age and RET/PTC rearrangement. In the separate analysis of the RET/PTC1 and RET/PTC3 subtypes, young people had nearly two-fold greater risk for RET/PTC3 rearrangement (Figure 4) but penetrance of the RET/PTC1 fusion gene was not affected. When radiation exposure was also considered, young people in the subpopulation with radiation exposure had higher risk for developing RET/PTC3...
rearrangement as compared to adults with radiation exposure. These positive associations were performed in a fixed-effects model and had slight inter-study heterogeneity (all Phet > 0.10).

**Association between RET/PTC fusion genes and sex**

Females are more likely to develop PTC, therefore we investigated whether female gender increases the chance of RET/PTC rearrangement in patients with PTC. As suggested by the findings in Table 5, sex was not statistically associated with RET/PTC status in the combined analysis. In subgroup analysis, a pooled analysis of 13 studies showed that female gender was associated with RET/PTC1 development in the subpopulation without radiation exposure. Female patients had 1.69-fold greater risk for RET/PTC1 rearrangement than male patients did (95%CI: 1.04–2.74; P = 0.034, Figure 5). However, female gender did not appear to play a role in RET/PTC3 rearrangement (all, P > 0.05). Only slight inter-study heterogeneity was observed in all of the above analyses (all Phet > 0.10).

**Heterogeneity testing and sensitivity analysis**

The inter-study heterogeneities in each comparison are presented in Tables 3–5. Pooled analyses for assessing the effect of radiation exposure and young age on the combined status of the RET/PTC1 and RET/PTC3 fusion genes demonstrated moderate heterogeneity. To explore the source of heterogeneity, subgroup analyses based on ethnicity and RET/PTC subtype were performed. Heterogeneity was decreased in the subgroup analysis and may be partly explained by the different ethnicities and RET/PTC subtypes (Tables 3 and 5).

Figure 1: Flowchart of literature search and selection of studies.
Table 1: Characteristics of studies included in the meta-analysis

| First author       | Year of publication | Ethnicity                        | Region | Method of detection | Radiation | No.of patients |
|--------------------|---------------------|----------------------------------|--------|---------------------|-----------|---------------|
| Nikiforov et al    | 1997                | Belarussian, Los Angeles,        | Western| RT-PCR              | Mixed     | 55            |
|                    |                     | Cincinnati                        |        |                     |           |               |
| Bounacer et al     | 1997                | French                            | Western| RT-PCR              | Mixed     | 39            |
| Motomura et al     | 1998                | Japanese                          | Asian  | RT-PCR              | Non-radiation | 21          |
| Smida et al        | 1999                | Belarussian, German               | Western| RT-PCR              | Mixed     | 83            |
| Rabes et al        | 2000                | Belarus, Russia, Ukrainian       | Western| PCR                 | Radiation | 191           |
| Elisei et al       | 2001                | Belarus, Itaian                   | Western| PCR                 | Mixed     | 89            |
| Puxeddu et al      | 2003                | Italian                           | Western| RT-PCR, Southern Blot | Non-radiation | 48          |
| Rhoden et al       | 2004                | American                          | Western| RT-PCR              | NM        | 25            |
| Nakazawa et al     | 2005                | Japanese                          | Asian  | RT-PCR              | Non-radiation | 169         |
| Brzezianska et al  | 2006                | Polish                            | Western| RT-PCR              | NM        | 33            |
| Hamatani et al     | 2008                | Japanese                          | Asian  | RT-PCR              | Mixed     | 71            |
| Tuttle et al       | 2008                | Russian                           | Western| RT-PCR              | Radiation | 76            |
| Lam et al          | 2002                | China, Hong Kong                  | Asian  | RT-PCR              | Non-radiation | 21          |
| Detours et al      | 2005                | Ukrainian                         | Western| RT-PCR              | Mixed     | 20            |
| Lima et al         | 2004                | Ukrainian                         | Western| RT-PCR              | Mixed     | 34            |
| Penko et al        | 2005                | American                          | Western| PCR                 | Mixed     | 13            |
| Romei et al        | 2008                | Italian                           | Western| RT-PCR              | Non-radiation | 70          |
| Hieber et al       | 2011                | Ukrainian                         | Western| FISH                | Radiation | 22            |
| Guerra et al       | 2014                | Italian                           | Western| RT-PCR              | NM        | 72            |
| Zou et al          | 2014                | Saudi Arabian                     | Asian  | RT-PCR              | NM        | 88            |
| Chung et al        | 1999                | Korean                            | Asian  | RT-PCR              | Non-radiation | 31          |
| Powell et al       | 2005                | Ukrainian                         | Western| PCR                 | Mixed     | 35            |
| Unger et al        | 2004                | Ukrainian                         | Western| FISH                | Radiation | 29            |
| Wang et al         | 2008                | Chinese                           | Asian  | RT-PCR              | Non-radiation | 126         |
| Nikiforova et al   | 2004                | Belorussian, Ukrainian            | Western| PCR                 | Mixed     | 137           |
| Basolo et al       | 2002                | Italian                           | Western| RT-PCR              | NM        | 91            |
| Rao et al          | 2014                | Indian                            | Asian  | RT-PCR              | Non-radiation | 30          |
| Collins et al      | 2002                | American                          | Western| IHC                 | Mixed     | 64            |
| Chung et al        | 2004                | Korean                            | Asian  | RT-PCR+IHC          | Non-radiation | 22          |
| Unger et al        | 2006                | Ukrainian                         | Western| FISH                | Radiation | 13            |

(Continued)
| First author     | Year of publication | Ethnicity           | Region | Method of detection | Radiation | No. of patients |
|------------------|---------------------|---------------------|--------|---------------------|-----------|----------------|
| Sadetzki et al   | 2004                | Israelis            | Asian  | RT-PCR              | Mixed     | 49             |
| Smyth et al      | 2005                | Irish               | Western| Taqman              | NM        | 34             |
| Learoyd et al    | 1998                | Australian, Swedish | Western| RT-PCR              | Mixed     | 50             |
| Nakazawa et al   | 2009                | Japanese            | Asian  | FISH+RT-PCR         | Non-radiation | 14          |
| Di Cristofaro et al | 2005          | Ukrainian, French   | Western| RT-PCR              | Mixed     | 50             |
| Erdogan          | 2008                | Turkish             | Asian  | RT-PCR              | Non-radiation | 101         |
| Fenton et al     | 2000                | American            | Western| PCR                 | Non-radiation | 33           |
| Guerra et al     | 2011                | Italian             | Western| RT-PCR              | NM        | 50             |
| Stanojevic et al | 2011                | Serbian             | Western| PCR                 | Non-radiation | 266         |

Table 2: Positive rates of **RET/PTC1** and **RET/PTC3** in each original study

| First author     | Year of publication | No. of PTC cases | Freq. of RET/PTC1 and 3(%) | RET/PTC1 and 3(%) | RET/PTC1(%) | RET/PTC3(%) |
|------------------|---------------------|------------------|-----------------------------|--------------------|-------------|-------------|
| **For Asian studies** |                     |                  |                             |                    |             |             |
| Motomura et al   | 1998                | 21               | 36.73%                      | 21.06%             | 26.50%      |             |
| Nakazawa et al   | 2005                | 169              | 28.40%                      | 25.44%             | 4.73%       |             |
| Hamatani et al   | 2008                | 71               | 16.90%                      |                    |             |             |
| Lam et al        | 2002                | 21               | 85.71%                      |                    |             |             |
| Zou et al        | 2014                | 88               | 13.64%                      | 13.64%             |             |             |
| Chung et al      | 1999                | 31               | 12.90%                      |                    |             |             |
| Wang et al       | 2008                | 126              | 14.29%                      |                    |             |             |
| Rao et al        | 2014                | 30               | 86.67%                      | 0.00%              | 86.67%      |             |
| Chung et al      | 2004                | 22               | 9.09%                       | 4.55%              | 4.55%       |             |
| Sadetzki et al   | 2004                | 49               | 44.90%                      | 40.82%             | 0.00%       |             |
| Nakazawa et al   | 2009                | 14               | 28.57%                      | 28.57%             | 0.00%       |             |
| Erdogan          | 2008                | 101              | 66.34%                      | 31.68%             | 20.79%      |             |
| **For Western studies** |                   |                  |                             |                    |             |             |
| Nikiforov et al  | 1997                | 55               | 42.19%                      | 25.25%             | 17.05%      |             |
| Bounacer et al   | 1997                | 39               | 46.15%                      | 38.46%             | 12.82%      |             |
| Smida et al      | 1999                | 83               | 46.99%                      | 31.33%             | 15.66%      |             |
| Rabes et al      | 2000                | 191              | 45.03%                      | 25.13%             | 19.90%      |             |
| Elisei et al     | 2001                | 89               | 44.94%                      | 20.22%             | 29.21%      |             |
| Puxeddu et al    | 2003                | 48               | 27.08%                      | 16.67%             | 10.42%      |             |

(Continued)
Sensitivity analysis was also conducted to assess the influence of individual studies on the overall risk of RET/PTC rearrangement by excluding any single study in turn and recalculating the pooled ORs and 95%CI. For the effect of radiation on RET/PTC rearrangement, Sadetzki et al. [21], Nakazawa et al. [22], and Bounacer et al. [24] reported greater differences in the risk estimates compared with other studies in the sensitivity analysis. Sensitivity analysis excluding the three studies generated a similar pooled OR of 3.30 (95%CI: 1.96–5.54, P < 0.001; I² = 32.1%, P = 0.142) among homogeneous studies. For the effect of young age on RET/PTC rearrangement, the outlier studies appeared to be the studies of Smida et al. (1999)[8] and Hieber et al. (2011)[35]. After removing the two studies, the heterogeneity was no longer significant (I² = 34.0%, P = 0.181), and similar estimates (OR = 1.10 vs. 1.53) were generated before and after these data were removed, indicating the relatively high stability of the results.

### Publication bias

Begg’s test and Egger’s test were performed to quantitatively evaluate the publication bias of the studies; the results are listed in Table 6. No significant publication bias was observed in all comparisons (all, P > 0.10).

### DISCUSSION

Previous study results on the relationship between PTC-related risk factors and RET/PTC rearrangement were controversial. To our knowledge, this is the first meta-analysis evaluating the effect of radiation exposure, female gender, and young age on RET/PTC rearrangement. By performing the present meta-analysis, we found that radiation exposure contributed to increased risk of RET/PTC rearrangement, especially for the RET/PTC3 subtype. Young age was also associated with higher prevalence of RET/PTC3, and this association was more

| First author     | Year of publication | No. of PTC cases | Freq. of RET/PTC1 and 3(%) | RET/PTC1(%) | Freq. of RET/PTC3 | RET/PTC3(%) |
|------------------|---------------------|-----------------|-----------------------------|-------------|-----------------|-------------|
| Rhoden et al     | 2004                | 25              | 18                          | 72.00%      | 18              | 72.00%      | 5           | 20.00%      |
| Brzezińska et al | 2006                | 33              | 7                           | 21.21%      | 11              | 14.47%      | 5           | 6.58%       |
| Tuttle et al     | 2008                | 76              | 13                          | 17.11%      | 11              | 5.00%       | 2           | 10.00%      |
| Detours et al    | 2005                | 20              | 7                           | 35.00%      | 1               | 41.18%      | 2           | 15.38%      |
| Lima et al       | 2004                | 34              | 14                          | 53.85%      | 5               | 38.46%      | 2           | 15.38%      |
| Penko et al      | 2005                | 13              | 7                           | 53.85%      | 5               | 38.46%      | 2           | 15.38%      |
| Romei et al      | 2008                | 13              | 18                          | 77.27%      | 13              | 18.57%      | 12          | 17.14%      |
| Hieber et al     | 2011                | 22              | 17                          | 16.67%      | 2               | 6.59%       | 3           | 10.34%      |
| Guerra et al     | 2014                | 72              | 12                          | 45.17%      | 6               | 6.59%       | 12          | 24.18%      |
| Powell et al     | 2005                | 35              | 16                          | 53.85%      | 5               | 38.46%      | 2           | 15.38%      |
| Unger et al      | 2004                | 29              | 5                           | 17.24%      | 2               | 6.90%       | 3           | 10.34%      |
| Nikiforova et al | 2004                | 137             | 48                          | 35.04%      | 16              | 11.68%      | 32          | 23.36%      |
| Basolo et al     | 2002                | 91              | 28                          | 30.77%      | 6               | 6.59%       | 22          | 24.18%      |
| Collins et al    | 2002                | 64              | 44                          | 68.75%      | 6               | 6.59%       | 22          | 24.18%      |
| Unger et al      | 2006                | 13              | 10                          | 76.92%      | 6               | 6.59%       | 22          | 24.18%      |
| Smyth et al      | 2005                | 34              | 13                          | 38.24%      | 10              | 29.41%      | 3           | 8.82%       |
| Learoyd et al    | 1998                | 50              | 4                           | 8.00%       | 4               | 8.00%       | 0           | 0.00%       |
| Di Cristofaro et al | 2005           | 50              | 30                          | 60.00%      | 26              | 52.00%      | 13          | 26.00%      |
| Fenton et al     | 2000                | 33              | 14                          | 42.42%      | 11              | 33.33%      | 3           | 9.09%       |
| Guerra et al     | 2011                | 50              | 18                          | 36.00%      | 3               | 15.79%      | 13          | 4.89%       |
| Stanojevic et al | 2011                | 266             | 55                          | 20.68%      | 42              | 15.79%      | 13          | 4.89%       |
significant in the subpopulation exposed to radiation. Our pooled estimate also demonstrated an association between female gender and higher prevalence of the \( \text{RET}/\text{PTC1} \) subtype in the subpopulation that had not been exposed to radiation. These results identify an enriched population of \( \text{RET}/\text{PTC} \) fusion genes in patients with PTC and provide novel insights into the utility of \( \text{RET}/\text{PTC} \) rearrangement in the differential diagnosis of suspicious PTC.

Exposure to ionizing radiation is a well-known risk factor for thyroid cancer, particularly for papillary carcinoma [48, 49]. Therefore, it is likely that radiation exposure may also be a causative factor for \( \text{RET}/\text{PTC} \) rearrangement. Our pooled estimates provide clear evidence that radiation exposure could be responsible for the difference in \( \text{RET}/\text{PTC3} \) prevalence between sporadic and radiation-associated tumors, whereas the rate of \( \text{RET}/\text{PTC1} \) prevalence was similar between the two groups. The corresponding pooled \( OR \) for \( \text{RET}/\text{PTC3} \) was up to 8.30, and this association was evident in the Western populations. However, we could not derive a negative or null association in the Asian population because of a lack of original studies from the Asian region. There are valid reasons to believe that there is a causative link between radiation exposure and \( \text{RET}/\text{PTC} \) rearrangements. For example, Nikiforov et al. reported much higher \( \text{RET}/\text{PTC3} \) prevalence in post-Chernobyl PTC than in subjects without radiation exposure [10]. In addition, \( \text{RET}/\text{PTC} \) rearrangement, predominantly \( \text{RET}/\text{PTC3} \), in thyroid cells, can be induced by ionizing radiation [50]. This may be linked to the particular effectiveness of radiation in causing double-strand breaks, which would be the direct cause of \( \text{RET} \) rearrangement [50, 51]. This mechanism may partially explain the association between radiation exposure and \( \text{RET}/\text{PTC} \) rearrangement in thyroid cancer.

The data synthesis in the present meta-analysis also demonstrated increased risk of \( \text{RET}/\text{PTC3} \) in PTC in young people. Our observations further indicate that young patients who exposed to radiation have higher \( \text{RET}/\text{PTC3} \) risk than young patients who have not been exposed to radiation. Original studies have shown that \( \text{RET}/\text{PTC3} \) is more common in children and adolescents compared to adults [8, 9]. When the radiation exposure effect was considered in young people, \( \text{RET}/\text{PTC3} \) was indicated as the most common form of rearrangement in radiation-associated childhood PTC [8, 10, 25, 52]. As the thyroid is very sensitive to radiation, the thyroid of young people might be more vulnerable to

### Table 3: Meta-analysis results for association between \( \text{RET}/\text{PTC} \) fusion genes and radiation exposure in patients with PTC

| Radiation exposure vs. non-radiation exposure | No. of studies | No. of cases/controls | OR(95%CI) | P value | Model | F | Phet* |
|---------------------------------------------|----------------|----------------------|---------|--------|-------|---|-------|
| For \( \text{RET}/\text{PTC1 and 3} \)     |                |                      |         |        |       |   |       |
| All                                         | 14             | 537/388              | 2.82(1.38,5.78) | **0.005** | Random | 74% | <0.001 |
| Region                                      |                |                      |         |        |       |   |       |
| Asian                                       | 4              | 232/71               | 0.88(0.26,2.93) | 0.833 | Random | 56% | 0.077 |
| Western                                     | 10             | 305/317              | **3.97(2.03,7.75)** | **<0.001** | Random | 59% | <0.001 |
| For \( \text{RET}/\text{PTC1} \)           |                |                      |         |        |       |   |       |
| All                                         | 9              | 285/287              | 1.86(0.66, 5.28) | 0.243 | Random | 76.00% | <0.001 |
| Region                                      |                |                      |         |        |       |   |       |
| Asian                                       | 1              | 37/12                | 0.24(0.06,0.96) | 0.043 | Random | / | / |
| Western                                     | 8              | 248/275              | 2.46(0.83,7.27) | 0.104 | Random | 74.10% | <0.001 |
| For \( \text{RET}/\text{PTC3} \)           |                |                      |         |        |       |   |       |
| All\(^b\)                                   | 8              | 243/240              | **8.30(4.32,15.96)** | **<0.001** | Fixed | 0.00% | 0.980 |
| Region                                      |                |                      |         |        |       |   |       |
| Asian                                       | /              | /                    | /       | /      | /     | / | /    |
| Western                                     | 8              | 243/240              | **8.30(4.32,15.96)** | **<0.001** | Fixed | 0.00% | 0.980 |

\(^a\), P-value for heterogeneity test;  
\(^b\), Data from Sadetzki et al. [21] and Learoyd et al. [6] showed that the \( \text{RET}/\text{PTC3} \) gene prevalence was 100% in both the groups with and without radiation exposure and that the \( OR \) and standard error could not be estimated; therefore, these studies were excluded. The statistically significant results are highlighted in bold.
Figure 2: Results of the association between RET/PTC1 and RET/PTC3 fusion genes and radiation exposure in patients with PTC.

Figure 3: Results of the association between RET/PTC3 fusion gene and radiation exposure in patients with PTC.
radiation than that of adults, which may result in higher RET/PTC prevalence in young people [53]. Nevertheless, it is important to consider that the statistical power in each original study may be partly determined by the cutoff value of age, such as age at diagnosis and age at exposure to radiation. When the cutoff age varies, the issue of the impact of patient age on RET/PTC rearrangement remains inconclusive, which would require further validation. By setting a cutoff age of 18 years in this meta-analysis, the corresponding results may indicate the relatively low defense ability of children against pathogenic factors.

Concerning the impact of sex, we observed that the association between female gender and increased RET/PTC1 risk was more significant in patients who had not been exposed to radiation. For unknown reasons, thyroid cancer is three times more prevalent in women than in men [54]. One possible explanation for this gender disparity is the hormonal differences between men and women. It has been documented that chromosome breaks and sister chromatid exchanges are elevated in women who are pregnant or taking oral contraceptives [55]. There is also evidence supporting the premise that RET/PTC is an estrogen-dependent gene required for breast cancer cell growth [56]. The above evidence suggests that some inherent differences render females more susceptible to RET rearrangements.

Nevertheless, this study has some limitations. First, although we included all available relevant articles in this meta-analysis, the sample sizes remain insufficiently large. Second, most studies in relation to the association between radiation exposure and RET/PTC3 were from the Western countries.

### Table 4: Meta-analysis results for association between RET/PTC fusion genes and age in patients with PTC

| Young people vs. adult | No. of studies | No. of cases/controls | OR(95%CI)     | P value | Model | I²   | Phet<sup>a</sup> |
|------------------------|---------------|-----------------------|---------------|---------|-------|------|------------------|
| **For RET/PTC1 and 3** |               |                       |               |         |       |      |                  |
| All                    | 8             | 187/332               | 1.10(0.56,2.16) | 0.783   | Random | 51.50% | 0.044           |
| Region                 |               |                       |               |         |       |      |                  |
| Asian                  | 2             | 41/149                | 1.76(0.84,3.69) | 0.133   | Fixed  | 4.30%  | 0.307           |
| Western                | 6             | 146/183               | 0.98(0.41,2.31) | 0.956   | Random | 54.50% | 0.052           |
| Radiation              |               |                       |               |         |       |      |                  |
| Radiation exposure     | 6             | 116/122               | 0.88(0.48,1.62) | 0.682   | Fixed  | 41.50% | 0.129           |
| Non-radiation exposure | 5             | 71/200                | 1.46(0.81,2.65) | 0.212   | Fixed  | 33.90% | 0.195           |
| **For RET/PTC1**       |               |                       |               |         |       |      |                  |
| All                    | 6             | 172/286               | 0.98(0.60,1.58) | 0.921   | Fixed  | 7.20%  | 0.370           |
| Region                 |               |                       |               |         |       |      |                  |
| Asian                  | 2             | 41/149                | 1.33(0.61,2.91) | 0.476   | Fixed  | 0.00%  | 0.466           |
| Western                | 4             | 131/137               | 0.81(0.44,1.50) | 0.507   | Fixed  | 21.40% | 0.282           |
| Radiation              |               |                       |               |         |       |      |                  |
| Radiation exposure     | 5             | 107/109               | 0.52(0.26,1.05) | 0.070   | Fixed  | 49.30% | 0.096           |
| Non-radiation exposure | 5             | 71/200                | 1.47(0.76,2.86) | 0.250   | Fixed  | 0.00%  | 0.574           |
| **For RET/PTC3**       |               |                       |               |         |       |      |                  |
| All                    | 7             | 179/318               | 2.03(1.14,3.62) | 0.017   | Fixed  | 46.70% | 0.081           |
| Region                 |               |                       |               |         |       |      |                  |
| Asian                  | 2             | 42/148                | 3.23(0.87,12.00) | 0.080   | Fixed  | 7.20%  | 0.299           |
| Western                | 5             | 137/170               | 1.84(0.97,3.50) | 0.206   | Random | 50.1%  | 0.091           |
| Radiation              |               |                       |               |         |       |      |                  |
| Radiation exposure     | 5             | 107/109               | 2.35(1.01,5.49) | 0.048   | Fixed  | 0.00%  | 0.574           |
| Non-radiation exposure | 5             | 72/199                | 1.68(0.28,10.01) | 0.570   | Random | 67.00% | 0.028           |

<sup>a</sup>, P-value for heterogeneity test. The statistically significant results are highlighted in bold.
thus the generalizability of our conclusions is limited. In the future, more studies are needed to confirm this association in Asian regions. Third, only two common \( RET/PTC \) subtypes, \( RET/PTC1 \) and \( RET/PTC3 \), were considered in this study, mainly due to the limitation of current laboratory techniques for simultaneously detecting all \( RET/PTC \) subtypes.

In conclusion, both radiation exposure and young age, i.e., age < 18 years, are associated with increased risk of \( RET/PTC3 \) rearrangement. In addition, female gender is associated with higher prevalence of the \( RET/PTC1 \) subtype in the subpopulation not exposed to radiation. We suggest that \( RET/PTC \) status in combination with radiation exposure, age, and sex should be considered when differential diagnoses are suggested for suspicious patients. Further large-scale studies concerning the relationship between radiation exposure and \( RET/PTC \) in the Asian population are required to confirm our meta-analysis results.

**MATERIALS AND METHODS**

**Search strategy**

We searched the PubMed, Web of Science, and Embase databases for all articles on the association between the \( RET/PTC \) fusion gene and PTC up to June 2015. The published date of available articles in this study was from 1959 to 2015. The keywords used for the search were “\( RET/PTC \)”, “\( RET/PTC \) fusion gene”, or “\( RET/PTC \) fusion oncoproteins” in combination with “Thyroid Cancer”, “Thyroid Carcinoma”, “Thyroid Neoplasms”, or “Thyroid Papillary Carcinoma”. The references of the articles acquired were also searched manually to broaden the search. When there was overlapping data, only the largest and most recent study was selected for this meta-analysis. If the data presented in an article were unclear, we contacted the author for specific raw data.

**Inclusion and exclusion criteria**

Eligible studies had to meet the following criteria: (1) the association between the \( RET/PTC \) fusion gene and the clinicopathological features of patients with PTC was explored; (2) PTC diagnosis was made according to the pathology results; (3) studies were full-text articles; and (4) there was sufficient data for estimating an odds ratio (OR) with a 95% confidence interval (CI). The exclusion criteria were: (1) duplicate publication; (2) article was an abstract, comment, review, conference proceeding, or editorial; (3) insufficient data were reported; and (4) study was not in English or Chinese.
The following items were collected: first name of first author; year of publication; population of study; number of enrolled patients; frequency of RET/PTC fusion gene; detection method; whether study subjects were children or adults; and clinicopathological features (sex, age, radiation history, and ethnicity). The above information was carefully extracted by two independent investigators (Xuan Su and Zhaoqu Li). If the two investigators could not reach a consensus, the result was reviewed by a third investigator (Caiyun He).

The strength of the association between RET/PTC and radiation exposure, age, and sex was estimated by OR and 95%CI. Two-sided P-values were evaluated in this meta-analysis, and P < 0.05 was considered statistically significant. The chi-square–based Q test and I² statistic were used to assess the statistical heterogeneity among studies. For the Q statistic, P < 0.10 was considered statistically significant for heterogeneity. When there was heterogeneity, a random-effects model based on the DerSimonian and Laird method was used to calculate the

Data extraction

| Female vs. male | No. of studies | No. of cases/controls | OR(95%CI)  | P value | Model | F | Phet |
|----------------|----------------|-----------------------|-----------|---------|-------|---|------|
| For RET/PTC1 and 3 | | | | |
| All | 27 | 1211/474 | 1.04(0.81,1.33) | 0.775 | Fixed | 0.00% | 0.938 |
| Region | | | | |
| Asian | 9 | 373/138 | 1.42(0.81,2.49) | 0.216 | Fixed | 0.00% | 0.754 |
| Western | 18 | 838/336 | 0.95(0.72,1.27) | 0.747 | Fixed | 0.00% | 0.934 |
| Radiation | | | | |
| Radiation exposure | 11 | 369/174 | 0.94(0.63,1.41) | 0.760 | Fixed | 0.00% | 0.941 |
| Non-radiation exposure | 17 | 721/258 | 1.28(0.90,1.82) | 0.171 | Fixed | 7.20% | 0.370 |
| For RET/PTC1 | | | | |
| All a | 16 | 832/324 | 1.21(0.87,1.69) | 0.256 | Fixed | 0.00% | 0.857 |
| Region | | | | |
| Asian | 5 | 213/62 | 0.98(0.48,2.01) | 0.962 | Fixed | 0.00% | 0.604 |
| Western | 11 | 619/261 | 1.28(0.88,1.87) | 0.193 | Fixed | 0.00% | 0.796 |
| Radiation | | | | |
| Radiation exposure | 4 | 185/104 | 1.22(0.70,2.11) | 0.482 | Fixed | 0.00% | 0.892 |
| Non-radiation exposure | 13 | 581/192 | 1.69(1.04,2.74) | 0.034 | Fixed | 0.00% | 0.768 |
| For RET/PTC3 | | | | |
| All,b | 17 | 785/304 | 0.87(0.60,1.27) | 0.466 | Fixed | 0.00% | 0.625 |
| Region | | | | |
| Asian | 5 | 155/40 | 1.54(0.59,3.99) | 0.378 | Fixed | 0.00% | 0.763 |
| Western | 11 | 619/261 | 0.77(0.51,1.17) | 0.223 | Fixed | 0.00% | 0.527 |
| Radiation | | | | |
| Radiation exposure | 4 | 185/104 | 0.82(0.45,1.48) | 0.504 | Fixed | 0.00% | 0.903 |
| Non-radiation exposure | 11 | 570/186 | 1.06(0.60,1.87) | 0.847 | Fixed | 0.00% | 0.696 |

a, P-value for heterogeneity test; b, Data from Rao et al. [7] and Detours et al. [31] showed that RET/PTC1 gene prevalence was 100% in both female and male groups and that the OR and standard error could not be estimated; therefore, these studies were excluded. The statistically significant results are highlighted in bold.

Data extraction

The following items were collected: first name of first author; year of publication; population of study; number of enrolled patients; frequency of RET/PTC fusion gene; detection method; whether study subjects were children or adults; and clinicopathological features (sex, age, radiation history, and ethnicity). The above information was carefully extracted by two independent investigators (Xuan Su and Zhaoqu Li). If the two investigators could not reach a consensus, the result was reviewed by a third investigator (Caiyun He).

Statistical analyses

The strength of the association between RET/PTC and radiation exposure, age, and sex was estimated by OR and 95%CI. Two-sided P-values were evaluated in this meta-analysis, and P < 0.05 was considered statistically significant. The chi-square–based Q test and F statistic were used to assess the statistical heterogeneity among studies. For the Q statistic, P < 0.10 was considered statistically significant for heterogeneity. When there was heterogeneity, a random-effects model based on the DerSimonian and Laird method was used to calculate the
Figure 5 Results of the association between RET/PTC1 fusion gene and female gender in PTC patients without radiation exposure.

Table 6: Analysis for publication bias

| Variable | Begg’s test | Egger’s test |
|----------|-------------|--------------|
|          | z value     | P value^a    | t value  | P value^a |
| For RET/PTC1 and 3 |             |              |          |            |
| Radiation exposure vs. non-radiation exposure | 0.93 | 0.352 | 1.34 | 0.205 |
| Female vs. male | 1.02 | 0.307 | 0.24 | 0.811 |
| Children and adolescent vs. adult | -0.25 | 0.805 | 0.16 | 0.882 |
| For RET/PTC1 |             |              |          |            |
| Radiation exposure vs. non-radiation exposure | 1.25 | 0.211 | 1.71 | 0.132 |
| Female vs. male | 0.27 | 0.787 | 0.15 | 0.879 |
| Children and adolescent vs. adult | -0.19 | 0.851 | 0.39 | 0.715 |
| For RET/PTC3 |             |              |          |            |
| Radiation exposure vs. non-radiation exposure | -0.56 | 0.573 | -1.75 | 0.156 |
| Female vs. male | 0.27 | 0.787 | 0.59 | 0.567 |
| Children and adolescent vs. adult | 0.45 | 0.652 | 1.92 | 0.113 |

^a, P value>0.1 was considered as no publication bias.
pooled OR of each study [57]; otherwise, a fixed-effects model based on the Mantel–Haenszel method was used [58]. Publication bias was examined using Begg’s and Egger’s tests [59, 60], where P < 0.10 was considered statistically significant. All analyses were performed using STATA 12.0. All tests were two-sided and the significance level was set at 0.05.

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CONFLICTS OF INTEREST

None declared.

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