Mutation Profile of Well-Differentiated Thyroid Cancer in Asians

Young Shin Song, Jung Ah Lim, Young Joo Park

Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea

Recent advances in molecular diagnostics have led to significant insights into the genetic basis of thyroid tumorigenesis. Among the mutations commonly seen in thyroid cancers, the vast majority are associated with the mitogen-activated protein kinase pathway. B-Raf proto-oncogene (BRAF) mutations are the most common mutations observed in papillary thyroid cancers (PTCs), followed by RET/PTC rearrangements and RAS mutations, while follicular thyroid cancers (FTCs) are more likely to harbor RAS mutations or PAX8/peroxisome proliferator-activated receptor γ (PPARγ) rearrangements. Beyond these more common mutations, alterations in the telomerase reverse transcriptase (TERT) promoter have recently been associated with clinicopathologic features, disease prognosis, and tumorigenesis in thyroid cancer. While the mutations underlying thyroid tumorigenesis are well known, the frequency of these mutations is strongly associated with geography, with clear differences reported between Asian and Western countries. Of particular interest is the prevalence of BRAF mutations, with Korean patients exhibiting the highest rate of BRAF-associated thyroid cancers in the world. Here, we review the prevalence of each of the most common mutations in Asian and Western countries, and identify the characteristics of well-differentiated thyroid cancer in Asians.

Keywords: Mutation; Thyroid neoplasms; Asia; Proto-oncogene proteins B-raf; Ret-PTC fusion oncoproteins; Oncogene proteins ras; PPAR gamma; Telomerase

INTRODUCTION

A number of genetic alterations have been shown to play a role in the development of follicular cell-derived thyroid cancer. These point mutations and translocations occur in genes of several important signaling pathways, particularly that of the mitogen-activated protein kinase (MAPK) pathway. The MAPK signaling pathway is a master regulator of numerous cellular processes including division, proliferation, differentiation, adhesion, migration, and apoptosis. B-Raf proto-oncogene (BRAF) mutations, RET/papillary thyroid cancer (PTC) rearrangements, and RAS mutations are the most common activators of the MAPK signaling pathway, with significant implications for thyroid tumorigenesis.

BRAF mutations are the most common mutations observed in PTCs, followed by RET/PTC rearrangements and RAS mutations, while follicular thyroid cancers (FTC) are more likely to harbor RAS mutations or PAX8/peroxisome proliferator-activated receptor γ (PPARγ) rearrangements. While all four of these mutations are common worldwide, the prevalence of each mutation type in thyroid cancer varies significantly, particularly between Asian and Western countries, with the prevalence of PTC significantly higher in Asian countries.

Beyond these more common mutations, alterations in the
telomerase reverse transcriptase (TERT) promoter may be predictive of clinicopathologic features, as well as disease prognosis and tumorigenesis in thyroid cancer. Like other common thyroid cancer mutations, the frequency of TERT promoter mutations also appear to differ among countries, though the significance of this observation remains limited due to the small number of studies on this mutation having been conducted to date.

In this article, we review the prevalence of each of the most common mutations in Asian and Western countries, and identify the characteristics of well-differentiated thyroid cancer (DTC) in Asians.

**BRAF MUTATION**

BRAF, located in chromosome 7, is the most commonly mutated gene in thyroid cancers, resulting in potent activation of the MAPK pathway. The most common mutational hotspot in BRAF is T1799A in exon 15, conferring a glutamate to valine substitution at amino acid 600 (V600E) in the BRAF protein. BRAF V600E is the most common genetic alteration in PTC, exhibiting high prevalence in classic PTC and the tall cell variant, although it is generally rare in the follicular variant. Because BRAF mutations can be detected preoperatively in fine needle aspiration biopsy (FNAB) specimens, it is often used in the diagnosis of PTC, and may inform initial treatment strategies. Furthermore, this mutation has emerged as a promising prognostic factor for PTC [1,2], although the prognostic value of this mutation is still inconclusive [3,4].

The overall prevalence of BRAF mutations is ~45% (range, 27.3% to 87.1%) [5,6], with prevalence significantly higher in

| Table 1. The Prevalence of BRAF Mutations in Papillary Thyroid Cancers |
|---------------------------------------------------------------|
| **Study** | **Country** | **Year** | **PTC** |
|---------------------------------------------------------------|
| **Asian total** | 6,108/8,884 (68.7) |
| Hong et al. (2014) [8] | Korea | 1995–2003 | 120/193 (62.2) |
| Jo et al. (2006) [10] | Korea | 2004–2005 | 102/161 (63.4) |
| Kim et al. (2009) [6] | Korea | 2005–2006 | 88/101 (87.1) |
| Kim et al. (2015) [11] | Korea | 2008–2012 | 2,497/3,019 (82.7) |
| Hong et al. (2014) [8] | Korea | 2009–2012 | 1,792/2,431 (73.7) |
| Takahashi et al. (2007) [12] | Japan | 1956–1993 | 38/64 (59.3) |
| Ito et al. (2009) [3] | Japan | 1996–2000 | 242/631 (38.4) |
| Xing et al. (2013) [2] | Japan | - | 33/49 (67.4) |
| Ito et al. (2014) [13] | Japan | 1996–2001 | 281/766 (36.7) |
| Guan et al. (2009) [7] | China | 1990–2007 | 639/1,032 (61.9) |
| Liu et al. (2014) [14] | China | 2011–2014 | 110/182 (60.6) |
| Lu et al. (2015) [15] | China | 2013–2014 | 121/150 (80.6) |
| Liu et al. (2005) [16] | Taiwan | 1997–2002 | 49/105 (46.7) |
| **American total** | 559/1,243 (45.0) |
| Jung et al. (2014) [9] | USA | 1974–2000 | 81/160 (50.6) |
| Kim et al. (2006) [17] | USA | 2000–2003 | 34/103 (33.0) |
| Jung et al. (2014) [9] | USA | 2009 | 70/169 (41.4) |
| Xing et al. (2013) [2] | USA | - | 316/691 (45.7) |
| Oler et al. (2009) [18] | Brazil | 2000–2007 | 58/120 (48.3) |
| **European total** | 1,470/3,475 (42.3) |
| Frasca et al. (2008) [19] | Italy | 2002–2005 | 125/323 (38.6) |
| Lupi et al. (2007) [20] | Italy | 2006 | 219/500 (43.8) |
| Basolo et al. (2010) [21] | Italy | 2006–2009 | 473/1,060 (44.6) |
| Xing et al. (2013) [2] | Italy | - | 266/551 (48.3) |
| Riesco-Eizaguirre et al. (2006) [22] | Spain | 2000–2003 | 28/67 (41.8) |
| Xing et al. (2013) [2] | Spain | - | 28/66 (42.4) |
| Sykorova et al. (2010) [23] | Czech Republic | 1960–2007 | 81/242 (33.5) |
| Xing et al. (2013) [2] | Czech Republic | - | 71/222 (32.0) |
| Goutas et al. (2008) [5] | Greece | - | 15/55 (27.3) |
| Musholt et al. (2010) [24] | Germany | 1988–2010 | 122/290 (42.1) |
| Xing et al. (2013) [2] | Poland | - | 42/99 (42.4) |

Values are expressed as number/total number (%).

PTC, papillary thyroid cancer.
Asia, especially Korea, relative to Western countries (Table 1) [2,3,5,6,7-24]. Although the mechanisms underlying this difference in BRAF mutation frequencies are not well understood, a recent theory suggests that these differences may be associated with higher iodine intake in the Asian populations. Average iodine intakes were 138 to 353 μg/day in the United States [25], 45.3 μg/day in Germany [26], and 226 and 163 μg/day for women and men, respectively, in the United Kingdom [27]. Meanwhile, Japanese and Korean iodine intakes far exceed that of most other countries: 1,565 μg/day in Japan [28] and 479 μg/day in Korea [29]. Furthermore, high iodine intake has been shown to be significantly associated with the occurrence of BRAF mutation [7], though exceptions do exist, including lower BRAF mutation rates in Japan relative to Korea. One possible explanation for this discrepancy may be that of chronic thyroiditis, which is more prevalent in the Korean population. In incidence of Hashimoto’s thyroiditis is strongly correlated with the development of PTC [30]. Because the prevalence of Hashimoto’s thyroiditis is high in Korea, this positive correlation may provide an explanation for the high incidence of PTC in this country. However, as Hashimoto’s thyroiditis is associated with genetic alterations other than BRAF mutations, such as rearrangements of RAS, ERK, and RET/PTC [31], the relationship between BRAF mutations in PTC and chronic thyroiditis requires further assessment.

While geographic differences in the incidence of BRAF mutations are well established, the prevalence of these mutations has changed over time. A recent publication from our laboratory revealed an increase in BRAF-associated thyroid cancers from 62.2% to 73.7% over the last two decades in Korea [8]. Similarly, in the United States, the overall prevalence of BRAF mutations remained stable for an extended period of time (~46%) but increased sharply from 50.0% to 76.9% in the classic papillary form of PTC over the last four decades [9]. More studies on the changes in the mutational rates and its clinical significance will be needed.

Table 2. The Prevalence of RAS Mutations in Well-Differentiated Thyroid Cancers

| Study               | Country | Year       | PTC       | FVPTC     | FTC        |
|---------------------|---------|------------|-----------|-----------|------------|
| Asian total         |         |            |           |           |            |
| Park et al. (1998)  | Korea   | 1995–1996  | 2/24 (8.3)| -         | -          |
| Jang et al. (2014)  | Korea   | 1990–2005  | -         | -         | -          |
| Kim et al. (2012)   | Korea   | 2006–2011  | -         | -         | -          |
| Park et al. (2013)  | Korea   | 2002–2013  | -         | -         | 16/35 (45.7)|
| Jeong et al. (2015) | Korea   | 2011–2012  | -         | 18/54 (33.3)| -          |
| Naito et al. (1998) | Japan   | 1974–1996  | 2/4/6 (8.3)| -         | -          |
| Fukushima et al. (2012)| Japan | 1990–2005 | -         | -         | 33/58 (56.9)|
| Kikuchi et al. (2013)| Japan | 2006–2011 | -         | -         | -          |
| Guo et al. (2014)   | China   | 2002–2011  | -         | -         | -          |
| Naito et al. (1998) | Taiwan  | 1975–1996  | 2/4/6 (8.3)| -         | -          |
| Liu et al. (2004)   | Taiwan  | 2006–2011  | -         | -         | -          |
| American total      |         |            |           | 62 (15.2) | 19/52 (36.5)|
| Namba et al. (1990)| USA     | 1975–1996  | 3/14 (21.4)| -         | -          |
| Garcia-Rostan et al.| USA     | 1975–1996  | 2/4/6 (8.3)| -         | -          |
| Nikiforova et al. (2003)| USA | 1975–1996 | 2/4/6 (8.3)| -         | -          |
| Zhu et al. (2003)   | USA     | 1975–1996  | 13/76 (17.1)| -         | -          |
| Jung et al. (2014)  | USA     | 1975–1996  | 4/149 (2.7)| -         | -          |
| Rivera et al. (2010)| USA     | 1975–1996  | 4/149 (2.7)| -         | -          |
| Jung et al. (2014)  | USA     | 1975–1996  | 4/149 (2.7)| -         | -          |
| European total      |         |            |           | 9/81 (11.1)| 17/58 (29.3)|
| Lemoine et al. (1989)| UK     | 1975–1996  | 3/14 (21.4)| -         | -          |
| Esapa et al. (1999)| UK      | 1975–1996  | 2/4/6 (8.3)| -         | -          |
| Basolo et al. (2000)| Italy   | 1975–1996  | 3/31 (9.7)| -         | -          |
| Vasko et al. (2003)| France  | 1975–1996  | 2/4/6 (8.3)| -         | -          |
| Di Cristofaro et al.| France  | 1975–1996  | 6/50 (12.0)| -         | -          |

Values are expressed as number/total number (%).
PTC, papillary thyroid cancer; FVPTC, follicular variant papillary thyroid cancer; FTC, follicular thyroid cancer.
RAS MUTATION

*RAS* mutations are the second most common genetic alteration in thyroid cancer. The *RAS* gene encodes a family of three isoforms: *NRAS*, *HRAS*, and *KRAS*. Thyroid neoplasms have been associated with mutations in all three isoforms of the *RAS* gene, although most studies have reported a predominance of *NRAS*61. *RAS* point mutations are commonly observed in FTC, as well as the follicular variant PTC. The frequency of *RAS* mutations in FTC ranges from 10.5% to 56.9% [32,33], and is slightly more common in Asia (45.6%) than in Western countries (36.5% in the Americas, and 29.3% in Europe). In contrast, the frequency of *RAS* mutations in PTC is much lower in Asia (Table 2) [9,32-52]. This low frequency of *RAS* mutations has remained relatively stable over time, which is likely to be due to the lower prevalence of follicular variant PTC in this population. In contrast, a study from the United States reported an increase in the proportion of *RAS*-positive thyroid cancers from 2.7% between 1974 and 2000 to 24.9% in 2009, due in part to an increase in the percentage of patients presenting with the follicular variant histology [9].

*RAS* mutations have been reported in the full spectrum of thyroid neoplasms, limiting the clinical diagnostic value of these mutations. Because it is difficult to differentiate specific types of follicular lesions in thyroid FNAB samples, the diagnostic use of *RAS* mutations in FNAB specimens remains controversial. The prognostic value of *RAS* mutations is also unclear, although some evidence suggests that *RAS*-positive thyroid cancers may be at risk for tumor dedifferentiation, a less favorable prognosis, and metastatic behavior, particularly with regard to bone metastasis [32,33].

**RET/PTC REARRANGEMENT**

Rearrangements of the *RET* proto-oncogene are commonly seen in PTC, and have been shown to play a role in disease pathogenesis. To date, 13 different types of *RET/PTC* rearrangements have been reported, though *RET/PTC1* and *RET/PTC3* account for more than 90% of all rearrangements. The relationship between radiation exposure and *RET/PTC* rearrangement has been established [53,54], with *RET/PTC* rearrangements in papillary thyroid cancers.

### Table 3. The Prevalence of *RET/PTC* Rearrangements in Papillary Thyroid Cancers

| Study | Country | Year | PTC* |
|-------|---------|------|------|
| Asian total | | | 46/279 (16.5) |
| Park et al. (1998) [34] | Korea | 1995–1996 | 0/24 (0.0) |
| Chung et al. (1999) [61] | Korea | 1996–1999 | 4/31 (12.9) |
| Ishizaka et al. (1989) [62] | Japan | - | 1/11 (9.1) |
| Namba et al. (1991) [56] | Japan | - | 0/10 (0.0) |
| Wajiwalku et al. (1992) [63] | Japan | - | 1/38 (2.6) |
| Motomura et al. (1998) [64] | Japan | 1987–1994 | 4/11 (36.4) |
| Nibu et al. (2005) [65] | Japan | - | 12/40 (30.0) |
| Lee et al. (1998) [57] | Taiwan | 1995–1996 | 6/11 (54.5) |
| Lam et al. (1998) [66] | Hong Kong | 1996–2000 | 17/40 (42.5) |
| Guo et al. (2014) [42] | China | 2010–2011 | 1/63 (1.6) |
| American total | USA | - | 166/622 (26.7) |
| Tallini et al. (1998) [67] | USA | - | 81/201 (40.3) |
| Rhoden et al. (2004) [58] | USA | - | 18/25 (72.0) |
| Jung et al. (2014) [9] | USA | 1974–2000 | 12/141 (8.5) |
| Jung et al. (2014) [9] | USA | 2009 | 4/169 (2.4) |
| Sugg et al. (1999) [68] | Canada | - | 51/86 (59.3) |
| European total | Germany | - | 71/403 (17.6) |
| Mayr et al. (1998) [59] | Germany | - | 8/99 (8.1) |
| Musholt et al. (2000) [69] | Germany | 1988–1999 | 17/119 (14.3) |
| Di Cristofaro et al. (2005) [60] | France | 1994–2003 | 9/21 (42.9) |
| Cinti et al. (2000) [70] | Italy | - | 13/69 (18.8) |
| Elisei et al. (2001) [54] | Italy | - | 11/47 (23.4) |
| Puxeddu et al. (2003) [71] | Italy | 1995–1999 | 13/48 (27.1) |

Values are expressed as number/total number (%).

PTC, papillary thyroid cancer.

*Post-chernobyl papillary thyroid cancers were excluded.*
rangements frequently observed in PTC patients who have received significant doses of external radiation, such as those affected by the Chernobyl nuclear accident. Elevated levels of childhood PTC are well documented in post-Chernobyl contaminated areas, accompanied by a high prevalence of RET/PTC rearrangements. Rapid proliferation of thyroid cells may account for the high sensitivity to radiation-induced RET/PTC rearrangements among children, although RET/PTC rearrangements also occur more frequently in children and young adults not exposed to radiation [55].

The prevalence of RET/PTC rearrangements in PTC varies widely in different populations (range, 0% to 86.8% [34,53,56]), with significant variability in mutational frequency even within the same geographical regions (0% to 54.5% in Asia [34,56,57], 2.4% to 72.0% in the Americas [9,58], and 8.1% to 42.9% in Europe [59,60]). These discrepancies may be due to the small size of the studies; when this variability is taken into account, the prevalence of RET/PTC rearrangements in Asia is generally low (16.5%) (Table 3) [9,34,42,54,56-71].

This wide range of the prevalence rates seen in these studies may reflect not only the geographic variability but also the effect of different detection methods. A variety of methods have been used to identify RET/PTC rearrangements, including reverse transcription polymerase chain reaction methods, Southern blot analysis, and fluorescence in situ hybridization. Zhu et al. [72] demonstrated that different detection methods could result in significant variability in the detection of RET/PTC rearrangement.

PAX8/PPARγ REARRANGEMENT

PAX8/PPARγ rearrangements occur as a result of an intrachromosomal translocation between most of the coding sequence of PAX8 (2q13) and the entire coding exons of PPARγ1 (3p25). The fusion gene appears to be an oncogene, and results in production of a PAX8/PPARγ fusion protein (PPFP). The PAX8/PPARγ fusion gene is most commonly found in FTC, the follicular variant PTC, and benign follicular adenomas, though the prevalence of these rearrangements varies significantly among studies. The mean frequency in FTC is 5.6% in Asia, 43.8% in the Americas, and 27.4% in Europe (Table 4) [36,38,45,46,73-84]. The low frequency of PAX8/PPARγ rearrangements in Asia is particularly noteworthy, with one Japanese study failing to identify a single PAX8/PPARγ rearrangement in FTC [73].

No evidence exists linking PAX8/PPARγ rearrangements with clinical outcomes in FTC. Multiple studies have reported no correlation between PAX8/PPARγ rearrangements and clinical variables such as gender, age, tumor size, lymph node me-

| Table 4. The Prevalence of PAX8/PPARγ Rearrangements in Well-Differentiated Thyroid Cancers |
|-----------------|--------|--------|--------|--------|--------|
| Study           | Country | Year   | PTC    | FVPTC  | FTC    |
| Asian total     |        |        |        |        |        |
| Kim et al. (2012) [36] | Korea | 1999–2004 | 0/12 (0.0) | - | 4/72 (5.6) |
| Jeong et al. (2015) [38] | Korea | 2002–2013 | - | - | 3/31 (9.7) |
| Hibi et al. (2004) [73] | Japan | 1989–2000 | 0/12 (0.0) | - | 0/6 (0.0) |
| American total  |        |        |        |        |        |
| Nikiforova et al. (2002) [74] | USA | - | - | - | 8/15 (53.3) |
| Nikiforova et al. (2003) [45] | USA | - | - | - | 13/33 (39.4) |
| French et al. (2003) [77] | USA | - | - | - | 11/42 (26.2) |
| Zhu et al. (2003) [46] | USA | - | 0/46 (0.0) | 0/30 (0.0) | - |
| Sahin et al. (2005) [75] | USA | 1996–2000 | - | - | 31/54 (57.4) |
| Giordano et al. (2006) [78] | USA | - | 0/51 (0.0) | - | 7/13 (53.8) |
| Nakabashi et al. (2004) [79] | Brazil | - | 0/9 (0.0) | - | 4/12 (33.3) |
| European total  |        |        |        |        |        |
| Dwight et al. (2003) [80] | Sweden | - | - | - | 46/169 (27.4) |
| Lacroix et al. (2005) [81] | France | - | - | - | 10/34 (29.4) |
| Di Cristofaro et al. (2006) [82] | France | - | 0/20 (0.0) | 1/12 (8.3) | 9/21 (42.9) |
| Castro et al. (2006) [83] | Portugal | - | - | 15/40 (37.5) | 12/27 (45.5) |
| Boos et al. (2013) [76] | Germany | - | - | 0/37 (0.0) | 6/49 (12.2) |
| Sahpaz et al. (2015) [84] | Turkey | 2001–2012 | - | - | 5/15 (33.3) |

Values are expressed as number/total number (%). PPARγ, peroxisome proliferator-activated receptor γ; PTC, papillary thyroid cancer; FVPTC, follicular variant papillary thyroid cancer; FTC, follicular thyroid cancer.
The prevalence of \textit{TERT} promoter mutation exhibits significant variability among countries ranging from 4.2\% to 25.5\% [89,92] of PTC and 5.9\% to 36.4\% [91,92] of FTC (Table 5) [88-97]. Among these, the Korean prevalence was noticeably lower than other countries. We analyzed 551 patients with DTC in our institution, with \textit{TERT} promoter mutations identified in 4.5\% of patients [92]. Among 222 DTCs treated at the Catholic University of Korea, the overall prevalence of \textit{TERT} promoter mutations was 5.4\% [93]. The relatively large proportion of small-size tumors in Korea may account for the low frequency of these mutations relative to other countries. \textit{TERT} promoter mutation assays are difficult to use in routine prognostic testing of DTC, especially in areas where its prevalence is low. Therefore, further studies identifying an optimal subset of \textit{TERT} promoter mutations may be warranted.

**CONCLUSIONS**

Recent advances in molecular diagnostics have led to significant insights into the genetic basis of thyroid tumorigenesis, including a number of genetic alterations involved in the development of follicular cell-derived cancers having been reported. The frequency of each of these mutations varies significantly among populations, with Asian residents exhibiting significantly different mutational profiles relative to Western countries. Korean populations often exhibit different mutation rates relative to other countries, with \textit{BRAF} mutation rates higher than other countries. Despite the lack of clinical associations, \textit{PPARγ} remains an attractive therapeutic target in thyroid cancer. Although \textit{PPARγ} agonists have shown promising results in both \textit{in vitro} and \textit{in vivo} studies [85,86], the results of these studies have been inconclusive. Larger studies with long-term follow-up will be needed to clarify the efficacy and availability of \textit{PPARγ} agonists in PPFP thyroid cancer.

\textbf{TERT PROMOTER MUTATION}

Somatic mutations in the \textit{TERT} promoter have been identified in many human malignancies including thyroid cancer. Mutations in the \textit{TERT} promoter have been shown to increase telomerase activity, which protects the telomere repeats from erosion and plays a key role in cellular immortality and tumorigenesis [87]. \textit{TERT} promoter mutations were mainly found in two hotspots, located −124 (chr5: 1,295,228C>T) and −146 bp (chr5: 1,295,250C>T) upstream of the gene transcription starting site. These mutations were recently shown to be more prevalent in aggressive thyroid cancers, and were associated with poor prognosis as well as high-risk clinicopathologic features [88-90]. Therefore, \textit{TERT} promoter mutation has received considerable attention as a novel prognostic biomarker. \textit{TERT} promoter mutations have been shown to coexist with other tumorigenic alterations, such as \textit{BRAF} or \textit{RAS} mutations. Indeed, the coexistence of \textit{BRAF} mutations and \textit{TERT} promoter mutations has been identified as an indicator of the worst prognosis [88,91].

The prevalence of \textit{TERT} promoter mutation exhibits significant variability among countries ranging from 4.2\% to 25.5\% [89,92] of PTC and 5.9\% to 36.4\% [91,92] of FTC (Table 5) [88-97]. Among these, the Korean prevalence was noticeably lower than other countries. We analyzed 551 patients with DTC in our institution, with \textit{TERT} promoter mutations identified in 4.5\% of patients [92]. Among 222 DTCs treated at the Catholic University of Korea, the overall prevalence of \textit{TERT} promoter mutations was 5.4\% [93]. The relatively large proportion of small-size tumors in Korea may account for the low frequency of these mutations relative to other countries. \textit{TERT} promoter mutation assays are difficult to use in routine prognostic testing of DTC, especially in areas where its prevalence is low. Therefore, further studies identifying an optimal subset of \textit{TERT} promoter mutations may be warranted.

**Table 5. The Prevalence of \textit{TERT} Promoter Mutations in Well-Differentiated Thyroid Cancers**

| Study                  | Country              | Year       | PTC       | FTC       |
|------------------------|----------------------|------------|-----------|-----------|
| Asian total            |                      |            |           |           |
| Song et al. (2015) [92]| Korea                | 1993–2012  | 57/840 (6.8) | 15/141 (10.7) |
| Jung et al. (2015) [93]| Korea                | -          | 18/432 (4.2) | 7/119 (5.9) |
| Liu et al. (2014) [91] | China                | -          | 12/222 (5.4)* | -          |
| American total         |                      |            | 39/408 (9.6) | 8/22 (36.4) |
| Liu et al. (2013) [94] | USA                  | -          | 91/764 (11.9) | 11/79 (13.9) |
| Xing et al. (2014) [88]| USA                  | 1990–2012  | 30/257 (11.7) | 11/79 (13.9) |
| European total         |                      |            | 61/507 (12.0) | -          |
| Liu et al. (2014) [89] | Sweden               | -          | 81/686 (11.8) | 37/216 (17.1) |
| Wang et al. (2014) [95]| Sweden               | 1986–2004  | 13/51 (25.5) | 8/36 (22.2) |
| Melo et al. (2014) [90]| Portugal, Spain      | -          | 25/332 (7.5) | 9/52 (17.3) |
| Muzzu et al. (2015) [96]| Italy                | -          | 22/182 (12.1) | 12/70 (17.1) |
| Gandolfi et al. (2015) [97]| Italy             | 1979–2013  | 21/121 (17.4) | 8/58 (13.8) |

Values are expressed as number/total number (%). 
TERT, telomerase reverse transcriptase; PTC, papillary thyroid cancer; FTC, follicular thyroid cancer.

*These data include both FTC and PTC, and are therefore not included in the total results.
than any other country, whereas RET/PTC and PAX8/PPARγ rearrangements, and TERT promoter mutations, are generally lower. Awareness of the role and prevalence of each mutation may be important for the design of future studies, and may hold promise as either a diagnostic tool or a therapeutic target.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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