Letter

Frequency of TERT Promoter Mutations in Real-World Analysis of 2,092 Thyroid Carcinoma Patients (Endocrinol Metab 2022;37:652-63, Heera Yang et al.)

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We have read the article by Yang et al. [1] with great interest. They investigated real-world frequencies of telomerase reverse transcriptase (TERT) promoter mutations (C228T [chr5: 1,295,228C>T] and C250T [chr5: 1,295,250C>T]) in patients with thyroid carcinoma. We congratulate the authors on their work for prospectively collecting data for the largest cohort of patients with thyroid cancers ever reported. The frequency of TERT promoter mutations in the real-world was lower than that of previous studies performed retrospectively. After we first reported the low-frequency of TERT promoter mutations in prospectively enrolled patients with papillary thyroid carcinoma (PTC) in 2020 [2], several institutions have reported their data on TERT promoter mutation frequency in real-world analysis [1,3,4]. Therefore, we aimed to summarize real-world data on TERT promoter mutations in thyroid cancers.

Data of TERT promoter mutations prospectively collected from consecutive patients with thyroid cancers were available in four studies (Table 1). As molecular diagnostic test of TERT promoter mutation became available for patients with thyroid cancer in Korea in late 2018, all studies conducted in Korea included patients who had undergone the molecular test after 2018. Meta-analysis showed that pooled proportion of TERT promoter mutations was 2.6% (95% confidence interval [CI], 2.1 to 3.2) in all PTCs, 1.3% (95% CI, 0.5 to 2.6) in PTCs ≤ 1.0 cm, and 5.6% (95% CI, 4.4 to 7.0) in PTCs > 1.0 cm (Table 1). There was no significant heterogeneity between studies (I²=0.0%) in the subgroup of PTCs > 1.0 cm. Consistently low prevalence in the prospective cohorts of PTC patients contradicts pooled proportion of 11.3% (95% CI, 9.3 to 13.5) from 13 studies included in a previous meta-analysis [5].

In PTCs > 1.0 cm, TERT promoter mutated cases were consistently associated with older age, larger size, lateral lymph node metastasis, and aggressive histologic features [1-3], in line with results from previous retrospective studies. On the other hand, there have been limited data on its prognostication role in PTCs ≤ 1.0 cm. Some studies have reported that status of TERT promoter mutation shows no association with aggressive clinicopathologic features in PTCs ≤ 1.0 cm, even in cases with co-existing BRAFV600E mutations [2,4]. However, only short-term follow-up has been done so far. A longer interval of surveillance for recurrence is required.

In conclusion, PTCs highly prevalent in Korea have a lower frequency of TERT promoter mutations than previously reported. The clinical utility of TERT promoter mutations as a prognostic marker has been validated in PTCs larger than 1.0 cm, but not in PTC ≤ 1.0 cm. We are grateful for the opportunity to...
review real-world data on frequency of TERT promoter mutations in patients with PTC.

**CONFLICTS OF INTEREST**

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

**ACKNOWLEDGMENTS**

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**REFERENCES**


### Table 1. Meta-Analysis of TERT Promoter Mutation Frequency in Prospectively Collected Patients with PTC

<table>
<thead>
<tr>
<th>Study</th>
<th>Data collection period</th>
<th>PTC, all</th>
<th>PTC ≤ 1.0 cm</th>
<th>PTC &gt; 1.0 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al. (2020) [2]</td>
<td>December 2018–December 2019</td>
<td>16/724 (2.2%)</td>
<td>5/518 (1.0%)</td>
<td>11/206 (5.3%)</td>
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<tr>
<td>Choi et al. (2021) [3]</td>
<td>February 2019–December 2020</td>
<td>13/622 (2.1%)</td>
<td>4/415 (1.0%)</td>
<td>9/207 (4.3%)</td>
</tr>
<tr>
<td>Lee et al. (2021) [4]</td>
<td>June 2019–October 2020</td>
<td>NA</td>
<td>16/504 (3.2%)</td>
<td>NA</td>
</tr>
<tr>
<td>Yang et al. (2022) [1]</td>
<td>January 2019–December 2020</td>
<td>57/2,020 (2.8%)</td>
<td>6/1,143 (0.5%)</td>
<td>51/877 (5.8%)</td>
</tr>
<tr>
<td>Total sample size</td>
<td>3,366</td>
<td>2,580</td>
<td>1,290</td>
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<tr>
<td>Pooled proportion (95% CI)</td>
<td>2.6% (2.1–3.2)%</td>
<td>1.3% (0.5–2.6)%</td>
<td>5.6% (4.4–7.0)%</td>
<td></td>
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<tr>
<td>Heterogeneity</td>
<td>$P=0.526, I^2=0.0%$</td>
<td>$P=0.001, I^2=81.1%$</td>
<td>$P=0.748, I^2=0.0%$</td>
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</tr>
</tbody>
</table>

TERT, telomerase reverse transcriptase; PTC, papillary thyroid carcinoma; NA, not available; CI, confidence interval; I, inconsistency.

*A fixed effect model was used for meta-analysis; *A random effect model was used for meta-analysis.