EnM
ENDOCRINOLOGY AND METABOLISM

Letter

Endocrinol Metab 2022;37:947-948
https://doi.org/10.3803/EnM.2022.1596
pISSN 2093-596X · eISSN 2093-5978

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.)

Sue Youn Kim[1], Chan Kwon Jung[1,2]

[1]Department of Hospital Pathology, [2]Cancer Research Institute, College of Medicine, The Catholic University of Korea, Seoul, Korea

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 (I^2=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 coexisting $BRAF^{V600E}$ 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

Received: 28 September 2022, **Accepted:** 4 October 2022

Corresponding author: Chan Kwon Jung
Department of Hospital Pathology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Korea
Tel: +82-2-2258-1622, **Fax:** +82-2-2258-1627, **E-mail:** ckjung@catholic.ac.kr

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

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

TERT, telomerase reverse transcriptase; PTC, papillary thyroid carcinoma; NA, not available; CI, confidence interval; I, inconsistency.
[a]A fixed effect model was used for meta-analysis; [b]A random effect model was used for meta-analysis.

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

This research was supported by a grant (NRF-2020R1F1-A1070028) from the Basic Science Research Program through the National Research Foundation funded by the Ministry of Science and ICT, Republic of Korea.

ORCID

Sue Youn Kim *https://orcid.org/0000-0003-0279-9787*
Chan Kwon Jung *https://orcid.org/0000-0001-6843-3708*

REFERENCES

1. Yang H, Park H, Ryu HJ, Heo J, Kim JS, Oh YL, et al. Frequency of TERT promoter mutations in real-world analysis of 2,092 thyroid carcinoma patients. Endocrinol Metab (Seoul) 2022;37:652-63.
2. Kim SY, Kim T, Kim K, Bae JS, Kim JS, Jung CK. Highly prevalent BRAF V600E and low-frequency TERT promoter mutations underlie papillary thyroid carcinoma in Koreans. J Pathol Transl Med 2020;54:310-7.
3. Choi YS, Choi SW, Yi JW. Prospective analysis of TERT promoter mutations in papillary thyroid carcinoma at a single institution. J Clin Med 2021;10:2179.
4. Lee J, Ha EJ, Roh J, Kim HK. Presence of TERT±BRAF V600E mutation is not a risk factor for the clinical management of patients with papillary thyroid microcarcinoma. Surgery 2021;170:743-7.
5. Bae JS, Kim Y, Jeon S, Kim SH, Kim TJ, Lee S, et al. Clinical utility of TERT promoter mutations and ALK rearrangement in thyroid cancer patients with a high prevalence of the BRAF V600E mutation. Diagn Pathol 2016;11:21.