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Thyroid Cancer, Iodine, and Gene Mutation

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Excessive iodine intake is associated with the development of papillary thyroid carcinoma and increases the expression of *BRAF* mutations. In order to prevent most patients with thyroid cancer from unnecessary treatment, it is important to distinguish the patients who need aggressive treatment from those who do not. Although conventional prognostic systems alone have limitations, adding molecular tests can more accurately predict the final outcome of each patient, because molecular changes precede histological changes. Although *BRAF* mutation has drawn much attention on its high prevalence, it cannot predict the clinical outcome of each patient. It was no longer significant after the adjustment with other prognostic factors. The isolated *BRAF* mutation may be a sensitive, but not specific marker of recurrence and mortality. Recently, telomerase reverse transcriptase (*TERT*) promoter mutation has been identified in thyroid cancer. It increases telomerase activity, which allows cancer cells to immortalize. It was found in 10 to 20% of differentiated thyroid carcinoma and more than 40% of dedifferentiated thyroid carcinoma. It is highly prevalent in old age, large tumor, aggressive histology, advanced stages, and distant metastasis. It is strongly associated with increased recurrence and mortality, therefore, aggressive treatment is required in patients with *TERT* promoter mutation. Concomitant *BRAF* and *TERT* promoter mutations show the most aggressive clinical outcomes. When ultrasonography shows nonparallel orientation and microlobulated margins, especially in those older than 50 years, there is a high probability of accompanying *TERT* promoter mutation. Inclusion of *TERT* promoter mutation analysis with conventional clinicopathological evaluation can lead to better prognostication and management for individual patients.

Key Words: Thyroid carcinoma, Iodine, *BRAF* mutation, *TERT* promoter mutation

Thyroid Cancer and Iodine

There are several environmental factors involved in the development of thyroid cancer. Among them, ionizing radiation is the most well-known environmental factor, followed by benign thyroid tumors and goiter, high TSH concentration, tall stature, obesity, and iodine.[1] Interestingly, smoking and alcohol drinking show an opposite relationship with the development of thyroid cancer.

Korea, along with Japan, is the country with highest iodine intake in the world. The average urinary iodine concentrations (UIC) of Japanese people in various regions range from 219 to 362 μg/L, and an average UIC of 1015 μg/L was reported in South Kayabe, Hokkaido.[2-4] In Korea, Kim et al.[5] in Yonsei Medical Center, reported that 278 Korean people consumed an average of 479 μg of iodine per day in 1998. Later, in 2019, Kim et al.[6] in Samsung Medical Center, reported that the average UIC of Koreans was 294 μg/L based on the National Health and Nutrition Examination Survey (2013-2015), belonging to the 'above requirement' according to World Health Organization iodine recommendation. This was the first epidemiological presentation targeting the entire population of Korea.

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They also pointed out that 14% belonged to iodine deficiency, while another 13% belonged to extreme iodine excess.

According to many epidemiological studies, follicular thyroid carcinoma (FTC) and anaplastic thyroid carcinoma (ATC) occur relatively frequently in iodine-deficient areas, and the occurrence of papillary thyroid carcinoma (PTC) increases rapidly when iodine is supplemented.[7-9] Areas with high iodine intake, such as Korea, have a relatively high incidence of PTC. In Korea, the prevalence of PTC was less than 80% of all thyroid cancer in 1980s, but gradually increased to 84% in the 1990s, 90% in the early and mid-2000s, 95% in the late 2000s, and 97% after 2010.[10-12] In fact, PTC accounts for 80-85% of the Western countries, but in Korea, approximately 97% of all thyroid cancers are PTC, and *BRAF* mutations are found in more than 80% of PTC.[13]

In 2017, Kim et al.[14] in Samsung Medical Center, reported that patients with thyroid cancer were more likely to be distributed in UIC <300 μg/L and in UIC ≥ 2500 μg/L than those with benign thyroid nodules (OR, 1.52 and 1.87, respectively). In 2018, Kim et al.[15] also investigated UIC for patients with PTC, and found that the frequency of *BRAF* mutation were higher in both patients with UIC ≥500 μg/L and UIC <300 μg/L, compared to those with UIC 300-500 μg/L (OR, 6.24 and 4.76, respectively). They also suggested that UIC was an independent predictor for *BRAF* mutations in PTC. In 2022, Zhang et al.[16] conducted a meta-analysis of 6544 people enrolled in 10 case-control studies. They reported that the group with UIC ≥300 μg/L was significantly associated with the occurrence of PTC (OR 4.05), but not with *BRAF* mutation or lymph node metastasis. On the other hand, the group consuming moderate iodine with UIC of 100-200 μg/L had a significant suppression of cancer occurrence (OR 0.36).

Then, can excessive iodine intake cause abnormal proliferation of thyroid cells or thyroid cancer? In 1992, Kanno et al.[17] reported that the development of nodular and neoplastic lesions in the thyroid gland increased as iodine intake was gradually increased in experimental rats. In 2000, Vitale et al.[18] reported that excessive iodine intake induces thyroid cell apoptosis by a mechanism independent of p53. In 2002, Boltze et al.[19] reported that PTC and FTC were developed at 110 weeks when 4 Gy of radiation was irradiated with sufficient iodine supply in experimental rats. In 2009, Guan et al.[20] investigated the relationship between *BRAF* mutation and iodine intake in PTC patients in China. The prevalence of *BRAF* mutation was significantly higher in any of the regions with high iodine content than any of the regions with normal iodine content (69% vs. 53%). Therefore, they suggested that high iodine intake seems to be a significant risk factor for the occurrence of *BRAF* mutation in thyroid gland and may therefore be a risk factor for the development of PTC. In 2016, Kowalska et al.[21] also reported that the prevalence of *BRAF* mutation in Polish patients with PTC increased as iodine supplementation increased in iodine-deficient areas. Taken together, therefore, excessive iodine intake causes abnormal proliferation of thyroid cells, followed by many genetic changes in dividing cells. A representative change is the occurrence of *BRAF* mutation. These genetic changes create a vulnerability to various carcinogens, and it can be thought that thyroid cancer will occur if radiation or oxidative stress is applied to these conditions.[22] In 2014, Wang et al.[23] reported that excessive iodine intake was associated with the development of thyroid cancer, and that it was also related to the development of aggressive thyroid cancer such as lymph node metastasis or advanced stage. However, a study conducted in Korea failed to prove the relationship between excessive iodine intake and an aggressive clinical feature in the patients with thyroid cancer.[14,15]

Thyroid Cancer and Gene Mutations

In order to prevent most patients with thyroid cancer from unnecessary treatment, it is important to distinguish patients who need aggressive treatment from those who do not. Conventional clinicopathological parameters have been used to predict the prognosis. However, they could not completely predict the final

outcome of each patient.[24] Therefore, more precise parameters for estimating the final outcome should be required.

Molecular changes, such as gene mutation, precede histological changes.[25] Therefore, molecular tests for genetic alterations in thyroid cancer may enhance the predictability of clinical outcomes. The Cancer Genome Atlas (TCGA) study[26] presented integrated genomic characterization of PTC in 2014. It reported the low frequency of somatic alterations in 496 PTCs compared to other cancers. Genetic alterations in PTC included point mutations (75%), gene fusions (15%), and copy number variations (7%). In patients with advanced stage, tumors may have more than one mutation.

The following description about the gene mutation was based on a paper published in the Endocrine Journal in 2020.[27]

BRAF Mutation in Thyroid Cancer

A *BRAF* mutation was firstly detected in human cancer in 2002.[28] Most cases activating *BRAF* mutation involve codon 600 and result in the V600E mutation, and a few cases of other *BRAF* mutations occur as K601E mutation, small in-frame insertions, deletions, or rearrangement.[29] The *BRAF* mutations were also found in thyroid cancer.[29-32] They have been reported in PTC and poorly-differentiated thyroid carcinoma (PDTC) or ATC arising from PTC, but not in FTC, medullary thyroid cancer (MTC) and benign thyroid tumor.[33] The prevalence of *BRAF* mutation in PTC ranges from 30% to more than 80%, depending on the iodine intake and geographic location.[20,34] *BRAF* mutation is known to be highly specific to PTC, but false-positive results have been rarely reported.[35] In Korea, approximately 97% of all thyroid cancers is PTC and more than 80% of PTC harbor *BRAF* mutation.[13] Therefore, molecular testing for the *BRAF* mutation in cytological specimen increases diagnostic sensitivity and accuracy in Korea.

The *BRAF* mutation has drawn much attention based on its high prevalence. Many studies have demonstrated that *BRAF* mutation is significantly associated with the aggressive clinicopathological characteristics of PTC, such as extrathyroidal extension, lymph node metastasis and advanced stages ad well as high recurrence and mortality rates.[32,33,36-39] However, many studies from East Asian countries including Taiwan, Korea, and Japan demonstrated that the *BRAF* mutation was not associated with disease-free survival as well as poor prognostic factors.[40-42] Many physicians wonder why thyroid cancer-related mortality is still extremely low, although the *BRAF* mutation is highly prevalent in patients with thyroid cancer. These findings suggest that the isolated *BRAF* mutation may be a sensitive, but not specific marker of tumor recurrence and mortality. In Korea, it plays a large role in increasing diagnostic accuracy. Recently, more specific markers predictive of aggressive behavior have emerged. Among them, a representative marker is telomerase reverse transcriptase (*TERT*) promoter mutation.

TERT Promoter Mutation in Thyroid Cancer

Telomeres are located at the ends of linear chromosomes. Telomere loss is most rapid early in life, and over a life span. As the cell divides, the telomeres get smaller. The cells finally become senescent and cell division stops. Shortened telomeres impair immune function that might also increase cancer susceptibility.[43] Therefore, telomere shortening can be related to the risk of cancer. Telomerase is a reverse transcriptase, and protects the telomere repeats from erosion. Therefore, it reverses telomere shortening. Telomerase is not expressed in normal cells, but is frequently activated in most cancer cells as well as stem cells.[44] Cancer cells are immortal because activated telomerase allows them to survive much longer than normal cell.

In 2013, point mutations of *TERT* promoter were firstly found in melanoma, and these mutations enhanced promoter activity by two- to four-fold, which could immortalize cancer cells by maintaining telomere length.[45,46] *TERT* promoter mutations have been identified in over 50 human cancers including thyroid cancer.[47] *TERT* promoter mutation has been shown to increase telomerase activity, which protects the telomere repeats from erosion and maintain telomere length. Two mutations in the *TERT* promoter (chr5:1295228C>T, termed

C228T, and chr5:1295250C>T, termed C250T) were found in melanoma.[45,46] These two mutations were detected in follicular cell-derived thyroid cancer but were absent in benign tumors and MTC.[48-50] These two mutations occurred in a mutually exclusive manner. C228T is far more dominant than C250T. The mutual exclusivity of the two mutations suggests that either may function sufficiently to play an important role in thyroid tumorigenesis although which one is more powerful oncogenically has not been established.[49,51] *TERT* promoter mutation was found in approximately 10% of PTC, 17% of FTC, and 40% of PDTC/ATC.[52] Among PTC, it was more prevalent in tall cell variant than conventional or follicular variants. The *TERT* promoter mutation has a significantly higher prevalence in old age, large tumor, aggressive histology, advanced stages, and distant metastasis.[52] *TERT* promoter mutation has not been found in childhood thyroid cancer, and were rarely found in small-sized thyroid cancer.[53] Yang et al.[54] suggested that *TERT* promoter mutation closely associated with non-radioiodine avidity in distant metastatic DTC. *BRAF* mutation has been known to be associated with iodine intake, but *TERT* promoter mutation is not.[55] In a multivariate comparison between the PTC with and without anaplastic transformation, *TERT* promoter mutation was independently associated with anaplastic transformation.[56] Collectively, PTC-derived ATCs are characterized by *BRAF* and *TERT* promoter mutations, and these mutations occur prior to anaplastic transformation. In a meta-analysis including 11 studies with 3911 patients, PTC with concurrent *BRAF* and *TERT* promoter mutations were associated with increased tumor aggressiveness and had worst prognosis in comparison with PTCs harboring *BRAF* or *TERT* promoter mutation alone.[57] Recently, Song et al.[58] suggested the potential mechanism of synergistic effect of *BRAF* and *TERT* promoter mutations on cancer progression. They explained that *BRAF* mutation activated MAPK pathway, and it upregulated E-twenty six (ETS) transcription factors. ETS factors bound to mutant *TERT* promoter, and it increased *TERT* promoter expression. The genotype of primary tumors has high concordance with the genotype of lymph node metastasis. However, distant metastases show enrichment in *TERT* promoter mutations and a decrease in *BRAF* mutations. Therefore, *TERT* promoter mutations may play a role in distant metastases.[59] *TERT* promoter mutation is also associated with increased mortality in PTC as well as other thyroid cancer. Liu et al.[60] reported that PTC with concurrent *BRAF* and *TERT* promoter mutations were associated with increased cancer-specific mortality in comparison with PTCs harboring BRAF or *TERT* promoter mutation alone (*TERT/BRAF* 22.7% vs. *TERT* 6.3% vs. *BRAF* 2.4% vs. wild type 0.6%). Kim et al.[52] evaluated the association of *TERT* promoter mutation with survival of 409 thyroid cancer patients followed for median 13 years. They reported that *TERT* promoter mutation was independently associated with poorer overall survival in patients with DTC (10-year survival, *TERT* promoter mutation 66% vs. wild type 98%) and in patients with PTC (74% vs. 99%). Concomitant *BRAF* and *TERT* promoter mutations worsened the survival rate of patients with PTC (10-year survival, both mutations 83% vs. wild type 99%; HR 5.62). Thereafter, several studies have supported the synergistic effects of concomitant *BRAF* and *TERT* promoter mutations.[55,61]

A few of studies investigated the association of *BRAF* and *TERT* promoter mutations with ultrasonography (US) findings. Hahn et al.[62] reported that PTC with *BRAF* mutation tended to show a nonparallel orientation (taller-than-wide) shape, but this finding was marginally significant (p=0.055). Kim et al.[63] reported that nonparallel orientation and microlobulated margin were independent US findings for predicting *TERT* promoter mutation in PTC, especially patients over 50 years. Therefore, they suggested that tests for *TERT* promoter mutation should be done when physicians met the unique US findings (nonparallel orientation and microlobulated margin) in thyroid nodular patients, especially over 50 years.

The dynamic risk stratification (DRS) system can predict the structural recurrence with higher accuracy than traditional predictive system based on clinicopathologic information.[64] In 2017, Kim et al.[65] developed a new integrative prognostic system that incorporates *TERT* promoter mutation into the DRS sys-

tem after initial therapy to better categorize and predict outcomes. They compared the new system with pre-existing DRS system and TNM classification using proportion of variance explained (PVE). Larger numbers of PVE suggest better predictability. They suggested that the PVE of new system to predict recurrence was higher than the pre-existing DRS system (22.4% vs. 18.5%). The PVE of new system to predict cancer-related death was also higher than pre-existing TNM system (11.5% vs. 7.4%). In 2022, Park et al.[66] found that cancer-specific survival (CSS) was significantly different in encapsulated angioinvasive (EA)-FTC patients stratified by *TERT* promoter mutations, but not in minimally invasive (MI)-FTC and widely invasive (WI)-FTC patients. They developed new groups as follows: Group 1 (MI-FTC, EA-FTC without *TERT*), Group 2 (WI-FTC without *TERT*), and Group 3 (EA-FTC with *TERT*; WI-FTC with *TERT*). Both PVE (22.44 vs. 9.63, respectively) and C-index (0.831 vs. 0.731, respectively) for CSS were higher in the new group than in the traditional WHO 2017 group. Likewise, both PVE (27.1 vs. 14.9, respectively) and C-index (0.846 vs. 0.794, respectively) for disease-free survival were also higher in the new group than in the WHO 2017 group. They suggested that the new group harmonizing of the WHO 2017 classification and *TERT* promoter mutation is effective in predicting CSS in FTC patients. Taking these results together, they concluded that inclusion of *TERT* promoter mutation analysis with conventional prognostic system could lead to better prognostication and management for individual patients.

Conflicts of Interest

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

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