The Prevalence of the BRAF(V600E) Mutation Is Increasing in Papillary Thyroid Cancers

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SUMMARY • • • • •

Background

Activating mutations in the RET/RAS/RAF/MAPK signal-transduction pathways have been reported in a majority of papillary thyroid cancers (PTC) in recent years. RET rearrangements have been associated with radiation-related PTC, but BRAF mutations have not. However, BRAF mutations are associated with more aggressive disease and a worse outcome. The purpose of the current report was to evaluate the frequency of the BRAF(V600E) mutations and RET/PTC rearrangements in a large series of patients with PTC over a period of 15 years and to correlate these findings with other demographic and clinical characteristics.

Methods and Results

Patients with PTC treated in several Italian centers during the period from 1996 to 2010 were included and divided into three consecutive 5-year periods. In three centers, there were 401 patients who had analysis of their PTC for BRAF and RET/PTC as well

as clinical and epidemiologic data. In addition, 459 patients with PTC from Sicily had only mutation analysis of the tumors. Individual and combined analysis of both groups showed a progressive increase in the frequency of BRAF mutations that was statistically significant. This was also true for the combined population of 860 patients. The prevalence of BRAF(V600E) mutations increased from 33.6% in 1996–2000 to 47.8% in 2001–2005 to 61.5% in 2006–2010 (P<0.0001) and the prevalence of RET/PTC rearrangements significantly decreased (P<0.0001) in the entire cohort.

During the 15-year period, there was a significant increase in age at diagnosis and a decrease in tumor size.

Conclusions

The oncogene profile of PTC has changed over the past 15 years, with a significant increase in the prevalence of BRAF(V600E) mutations and a decrease in RET/PTC rearrangements.

ANALYSIS AND COMMENTARY • • • • •

The results in the current report from Italy confirm a report from California covering the period 1991–2005 in three 5-year periods; the prevalence of BRAF increased from 43% in the first 5-year period to 88% in the third (1) (reviewed in Clinical Thyroi-

dology, July 2011). In a smaller cohort from Ireland of patients with PTC, an increase in prevalence of the BRAF mutation was found in tumors after 1997 versus those removed before 1997 (2).

For many years, it has been noted that iodine procontinued on next page





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phylaxis was associated with an increase in the ratio of papillary to follicular thyroid cancers. It should be noted that the mutations discussed above are found in PTC and not in follicular thyroid carcinoma. A higher prevalence of BRAF mutation was reported in regions of China with higher iodine intake as compared with regions with lower iodine intake (3). However, in the United States, the intake of iodine has been sufficient for many decades, so it

is unlikely that higher iodine intake can explain the increased prevalence of the BRAF mutation in PTC. It is possible that thus far unrecognized environmental pollutants damage DNA, cause BRAF mutations, and are responsible for thyroid carcinogenesis, but this remains to be demonstrated.

- Jerome M. Hershman, MD

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