Oncogenesis and Genetic Screening of Medullary Thyroid Carcinoma

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Medullary thyroid carcinoma (MTC) is a neuroendocrine tumor originated from the parafollicular C cells of the thyroid gland. MTC accounts for approximately 3 to 5 percent of thyroid carcinomas in Western counteries, however in Korea the incidence is known to be less than 1−2%. Most (80%) medullary thyroid carcinomas are sporadic. However, some are familial as part of the multiple endocrine neoplasia type 2 (MEN2) syndrome. MEN2 is subclassified into three distinct syndromes, each of which is transmitted in an autosomal dominant fashion and is associated with MTC: MEN2A; MEN2B; and familial medullary thyroid cancer (FMTC). MEN2A is associated with MTC, pheochromocytoma, and primary parathyroid hyperplasia. MEN2B shares the inherited predisposition to MTC and pheochromocytoma present in MEN2A, but does not include hyperparathyroidism. FMTC is a variant of MEN2A, in which there is a strong predisposition to MTC but not the other clinical manifestations of MEN2A (or 2B). These syndromes result from different mutations in the RET proto-oncogene. Modern molecular techniques for genetic screening for the RET proto-oncogene permit the precise identification of the risk for MTC. Preventive thyroidectomy in patients screened early for germline RET gene mutations allows for earlier diagnosis and treatment of patients, sometimes before any hyperplasia or neoplasia can be demonstrated. An important question is what proportion of patients with apparently sporadic MTC have unsuspected germline RET mutations (the underlying defect in MEN2) and, therefore, heritable disease. Studies examining unselected patients with MTC have found that 6 to 7 % carry germline mutations. In one report, 35 of 482 patients (7.3%) with apparently sporadic MTC had mutations, and in 18 of these 35, gene carriers were identified in relatives. About 75% of the familial medullary cases are known to have no prior family history. The diagnostic yield of genetic screening, with its attendant potential for crucial clinical benefit, seems sufficiently high to justify the cost of RET mutational screening in all patients with apparently sporadic MTC. A much higher percentage (about 50 percent) of patients with sporadic MTC have somatic (acquired) mutations in the RET gene. These mutations are present only in the tumor cells, and are not detected in leukocyte DNA. Therefore the debates are still going on the strategy of appropriate genetic screening in patients with high or low risk for MTC.