Ulusal Cer Derg 2014; 30: 62-66
DOI: 10.5152/UCD.2014.125092014

Controversies in familial thyroid cancer 2014

Ailesel tiroid kanseri hakkında tartışmalı konular 2014

Orlo H. Clark

ABSTRACT

Thyroid cancer is the sixth most common cancer in women, and the majority of patients with thyroid cancer has sporadic disease. However, about 25% of patients with medullary thyroid cancer and 5% with papillary thyroid cancer have familial tumors. Currently, there are numerous controversies regarding the mode of inheritance, tumor behavior, extent of surgical resection for optimal results, coexisting thyroid pathology, risk of other cancers, and extent of postoperative treatment of patients with familial thyroid cancer. This review aimed to give insight to surgeons on this interesting topic.

Key Words: Thyroid, cancer, familial, papillary, medullary

ÖZET

Tiroid kanseri kadınlarda en sık görülen kanserler arasında altıncı sıradadır ve tiroid kanserli hastaların çoğunda sporadik hastalık mevcuttur. Bununla birlikte, medüller tiroid kanseri hastalarının yaklaşık yüzde 25'inde ve papiller tiroid kanseri hastalarının yüzde 5'inde ailesel tümör vardır. Güncel olarak; kalıtım şekli, tümör davranışı, optimal sonuçlar için tümör rezeksiyonunun derecesi, beraberinde bulunan tiroid patolojisi, diğer kanser riskleri ve ailesel tiroid kanseri hastalarının postoperatif tedavi miktarı açısından birçok tartışma vardır. Bu derleme bu ilginç konu hakkında cerrahlara bilgi vermeyi amaçlamıştır.

Anahtar Kelimeler: Tiroid, kanser, ailesel, papiller, medüller

Thyroid cancer is the sixth most common cancer in women and the second most common cancer in women under 40 years of age. Approximately 56,400 new patients will be diagnosed with thyroid cancer in 2013 in the United States. Thyroid cancer is also the most rapidly increasing cancer in the USA, and although most patients, with appropriate treatment, have a good prognosis, some patients unfortunately die from the spread of this tumor (1). Thyroid cancer usually originates from follicular thyroid cells (papillary, follicular, Hurthle cell cancer) or from parafollicular cells (medullary thyroid cancer).

The majority of patients with thyroid cancer has sporadic disease, although about 25% of patients with medullary thyroid cancer and 5% with papillary thyroid cancer have familial tumors (2, 3). Of interest is that in the United States and Europe, studies document a higher genetic predisposition to thyroid cancer than for any other tumor. Familial follicular thyroid cancer is quite rare (4).

Thyroid cancer is reported to be three to nine times more common in families having other members with thyroid cancer. It is also more common in patients with a history of exposure to low-dose therapeutic radiation (5). Young children are at highest risk of developing thyroid cancer after radiation exposure, and the risk of thyroid cancer increases as the dose of radiation increases from 6 to 2000 rads (6). Higher doses of radiation tend to eliminate the thyroid cells, so that hypothyroidism is common in patients exposed to high doses of radiation, but thyroid cancer is not. Adults up to age 50 at the time of exposure are also at increased risk of thyroid cancer after radiation, but this risk is smaller (7). Other malignant tumors appear to be more common in patients with familial papillary thyroid cancer (FPTC), including breast cancer in women and prostate cancer in men, as well as sarcoma, leukemia, and colon cancer (8). Currently, there are numerous controversies regarding the mode of inheritance, tumor behavior, extent of surgical resection for optimal results, coexisting thyroid pathology, risk of other cancers, and extent of postoperative treatment of patients with cancer FPTC.

Familial Medullary Thyroid Cancer

Familial medullary thyroid cancer, associated with multiple endocrine neoplasia, was first reported by John Sipple in 1961 and has been referred to as Sipple's syndrome (9). In 1966, Williams and Pollock (10) in London reported two patients with neuromatosis, pheochromocytomas, and thyroid cancer. A year earlier, Williams had reported 17 cases of thyroid cancer and pheochromocytoma (11). In 1968, Alton Steiner and colleagues (12) described a kindred of 168 patients with pheochromocytomas, medullary thyroid cancer, and parathyroid tumors and one patient with Cushing's disease. They believed that this syndrome, MEN type 2, was distinct from MEN type 1 and was inherited as an autosomal dominant gene

Professor Emeritus of Surgery, Division of General Surgery, San Francisco, USA

Address for Correspondence
Yazışma Adresi
Orlo H. Clark, M.D.
Professor Emeritus of Surgery, Division of General Surgery, San Francisco, USA
e-mail: orloherrickclark@gmail.com

Received / *Geliş Tarihi*: 10.03.2014
Accepted / *Kabul Tarihi*: 04.05.2014

©Copyright 2014
by Turkish Surgical Association

Available online at
www.ulusalcerrahidergisi.org

©Telif Hakkı 2014
Türk Cerrahi Derneği

Makale metnine www.ulusalcerrahidergisi.org web sayfasından ulaşılabilir.

with high penetrance. In 1980, Glen Sizemore and colleagues recognized that MEN2 had two variants, which he designated MEN 2A and MEN 2B (13). In 1986, John Farndon et al. (14) described a third variant of familial MTC that had patients with MTC without other endocrinopathies. Of interest was that patients with isolated familial MTC had the least aggressive medullary thyroid cancers, whereas patients with MEN 2B had the most aggressive tumors, with earlier onset, more invasive tumors, distant metastases, and higher tumor-related mortality.

Subsequent studies documented that there are genotype/phenotype correlations in patients with familial and sporadic MTC (15). All patients with MTC should be screened for a RET mutation, since about 50% of patients with MEN 2B and about 10% of patients with MEN 2A or familial MTC have a de novo RET mutation. This means that although their parents and siblings do not have a RET mutation, half of their children are at risk for MTC. Total thyroidectomy is recommended to most patients with a family history of MTC who are RET-positive, prior to age 6 or earlier, if there are thyroid nodules or the patient has an increased blood calcitonin level.

Familial Non-Medullary Thyroid Cancer

Familial non-medullary thyroid cancer (FNMTC) is defined as occurring in patients having well-differentiated thyroid cancer of follicular cell origin in two or more first-degree relatives. Most patients with FNMTC have familial papillary thyroid cancer (FPTC), as first reported in identical twins by Robinson and Orr in 1955 (16). Similar to familial MTC, FPTC occurs as an isolated tumor, which is often multifocal, associated with coexisting benign thyroid tumors, or is associated with other syndromes (17). Numerous genetic abnormalities are associated with sporadic papillary thyroid cancers. RET/PTC rearrangements were the first genetic abnormalities to be associated with the development of sporadic papillary thyroid cancers (18). RET rearrangements occur most often in papillary thyroid cancers associated with radiation exposure and in children (19). RET/PTC 1 and 3 rearrangements are the most frequent mutations, and 15 RET rearrangements have been documented (19). RET/PTC mutations have been reported to be associated with both more and less aggressive thyroid cancers but probably do not influence tumor behavior (20). A BRAF point mutation is the most common abnormality in sporadic PTC and is found in about 50% of these tumors (21). BRAF mutations are more common in poorly differentiated thyroid cancers, more invasive PTC, and PTCs with lymph node metastases (22, 23). Most but not all reports suggest that a BRAF mutation is associated with a worse prognosis. In some medical centers, however, up to 80% of papillary thyroid cancers have a BRAF mutation, thus decreasing its prognostic value.

RAS somatic mutations are reported to be more common in follicular thyroid cancers than in papillary thyroid cancers in most but not all studies (24, 25). RAS mutations are also found in some benign thyroid tumors (25). TRK mutations are found in about 5% to 15% of PTCs (26). Pax 8/PPAR gamma mutations are most often identified in follicular thyroid cancers but also occur in follicular adenomas (27). p53 mutations are almost exclusively found in anaplastic thyroid cancers and in thyroid cancer cell lines (28). They may also be present in poorly differentiated thyroid cancers. One might question whether the same somatic mutations that are responsible for sporadic thyroid tumors also cause familial thyroid cancers of follicular cell origin, but this does not appear to be the case (29).

Table 1. Genetics of familial non-medullary thyroid cancer

	Chromosome*	Author
Familial multinodular goiter	14q31	Bignell et al. (30)
Thyroid cancer with oxyphilia	19p13.2	Canzian et al. (31)
PTC with papillary renal neoplasia	1q21	Malchoff et al. (32)
Follicular variant of PTC	2q21	McKay et al. (33)
PTC	8p23. 1-p22	Cavaco et al. (42)
PTC	1q21&6q22	Suh et al. (40)

*pertinent gene not identified; PTC: papillary thyroid cancer

Table 2. Genetics and inheritance in familial syndromes with non-medullary thyroid cancer

Syndromes	Gene	Chromosome	Inheritance
Familial adenomatous polyposis	APC	5q21	AD
Cowden's disease	PTEN	10q22-23	AD
Werner's syndrome (in Japanese)	WRN	8p11-21	AR
Carney's complex	PRKAR1a	17q24	AD
McCune-Albright syndrome	GNAS1	20q13.1-13.2	Mosaic

AD: autosomal dominant; AR: autosomal recessive

Germline mutations have been documented in a Canadian family with familial goiter, (30) in a French family with trabecular and oxyphilic thyroid cancer and nodular goiter, (31) in one family with PTC and papillary renal neoplasia, (32) and in a Tasmanian family with a familial follicular variant of PTC (33) (Table 1). Thyroid cancer is also more common in patients with familial polyposis, (34) Cowden's syndrome, (35) Werner's syndrome, in Japanese people, (36) McCune-Albright syndrome (37) and in Carney's syndrome (38) (Table 2). Other possible linkage sites for FPTC not associated with other syndromes have been found on chromosomes 8p23.1-p22, 8q24, 1q21, and 6q22 (39-42). The gene or genes responsible for most cases of FPTC have not been identified. MicroRNA markers, such as MIR-886-3p, that help regulate cell proliferation and migration are deregulated in FPTC (43). Unfortunately, prophylactic thyroidectomy, directed by genetic testing, currently can not be recommended to remove the thyroid gland in patients who are genetically predisposed to developing FPTC.

In 2008, Capezzone et al. (44) reported "short telomeres, telomere reverse transcriptase gene amplification, and increased telomerase activity in the blood of familial papillary thyroid cancer patients." He et al. (45) also reported that "telomere length is shorter in affected member of families with familial non-medullary thyroid cancer." Cantara et al. (46) likewise reported "telomere abnormalities and chromosome fragility in patients affected by familial papillary thyroid cancer." Jendrzejewski et al. (39), in contrast, failed to find any differences in telomere length or TERT copy number in patients with FNMTC.

Tumor Behavior

Retrospective studies by Grossman et al. (4), Alsanea et al. (47), Uchino et al. (41), Triponez et al. (48), Mazeh et al. (49), and Park et al. (50) suggest that FPTC is more aggressive than sporadic papillary thyroid cancer. FNMTC is also more likely to be multifocal, invasive, and metastatic and associated with lymph node metastases and has a higher recurrence rate. Other investigators, however, report that it is not more aggressive, including Loh et al. (51), Maxwell et al. (52), Ito et al. (53), Robenshtok et al. (54), and Moses et al. (55). Lupoli et al. (56) studied seven patients from six families with FPTC and reported that even familial microcarcinomas can behave in an aggressive manner. We have also observed patients with small primary thyroid cancers who unfortunately had bone and pulmonary metastases. Some family members with FPTC also have developed anaplastic thyroid cancer. Alsanea et al. (47) and Triponez et al. (48) reported that patients with three or more members with FPTC were more likely to die from their thyroid cancer than those with just two documented patients with thyroid cancer or patients without thyroid cancer. Index cases had a higher death rate than subsequent family members (48). Charkes (57) published that the likelihood is 31% to 38% that at least one of a pair of family members with non-medullary thyroid cancer has an inherited disorder. When three or more patients have papillary thyroid cancer in the same family, 96% has familial disease. These findings may help explain the differences reported by many groups regarding tumor aggressiveness, since many of these patients with only two members with thyroid cancer probably have sporadic rather than familial disease. Most studies suggest that at least in families with three or more members, an autosomal dominant mode of inheritance is present, with incomplete expression (58). Others studies suggest that a polygenetic etiology is also possible (59).

Clinical Management of FPTC

The clinical evaluation of patients with FPTC appears to be similar to that for most patients with a thyroid nodule. In family members of patients with FPTC who have a normal thyroid gland documented by physical examination, an ultrasound examination is recommended beginning at age 10. When a suspicious nodule or nodules are identified, fine needle aspiration biopsy for cytological examination is recommended. Needle biopsy, however, is not as accurate in patients with FPTC because of the multifocal nature of these tumors, and coexisting benign thyroid nodules are also more common than in patients with sporadic thyroid tumors (60). One 9-year-old boy with FPTC has been reported with widely metastatic disease (61).

For patients with thyroid cancer or a suspicious thyroid biopsy, total thyroidectomy is recommended. Lymph node metastases are more common in these patients, so nodal metastases should be searched for on ultrasound and at the operation and removed if observed. Patients should also be carefully examined for other cancers, since such tumors are somewhat more common in these patients.

Genetic Testing

Some patients have concerns or fears about genetic testing, and consultation with a genetic counselor is recommended. When testing for genetic disease, one should first examine patients who have documented disease before testing other family members without documented thyroid cancer. Although genetic testing raises many ethical questions, to date, genetic discrimination by health insurers has not been a problem, according to the American Society of Human Genetics. There is still the fear of loss of confidentiality and genetic discrimination or of finding unrelated genes that predispose one to other disorders. The main question to be addressed is how this information should benefit most patients or their family members, especially when early treatment may save lives.

Capazzone (44) and colleagues, as previously mentioned, reported that there are short telomere lengths, hTERT gene amplification, and increased telomerase expression in familial thyroid cancers. There may also be genetic anticipation. Although not all others have been able to repeat these findings, genetic anticipation has been reported to occur in some neurologic diseases where the children present with the same disease as their parents but at an earlier age or with more extensive disease.

CONCLUSION

About 5% of patients with thyroid cancer have familial thyroid cancer, and most of these patients have familial papillary thyroid cancer. The molecular mechanisms responsible for these tumors are unknown for most of these patients, and more research studies should be done. It appears that FPTC is slightly more aggressive than sporadic PTC, and coexisting benign thyroid tumors are more common, as are other non-thyroidal tumors.

Peer-review: This manuscript was prepared by the invitation of the Editorial Board and its scientific evaluation was carried out by the Editorial Board.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Hakem değerlendirmesi: Bu makale Editörler Kurulu'nun davetiyle hazırlandığından bilimsel değerlendirmesi Editörler Kurulu tarafından yapılmıştır.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

REFERENCES

1. Sippel RS, Mazeh H. Familial non medullary thyroid carcinoma. Thyroid 2013; 23: 1049-1056. [CrossRef]
2. Kebebew E Greenspan FS, Clark OH, Woeber KA, Grunwell J. Extent of disease and practice patterns for medullary thyroid cancer. J Am Coll Surg 2005; 200: 890-896. [CrossRef]
3. Sturgeon C, Clark OH. Familial non medullary thyroid cancer. Thyroid 2005; 15: 588-593. [CrossRef]
4. Grossman RG, Tu SH, Duh QY, Siperstein AE, Novosolof F, Clark OH. Familial non medullary thyroid cancer an emerging entity that warrents aggressive treatment. Arch Surg 1995; 130: 892- 899. [CrossRef]
5. Pal T, Vogl FD, Chappuis PO, Tsang R, Brierly J, Renard H, et al. Increased risk for non medullary thyroid cancer in first degree relatives

of prevalent cases of non medullary thyroid cancer: a hospital- based study. J Clin Endocrinol Metab 2001; 86: 5307-5312. [CrossRef]
6. Greenspan FS. Radiation exposure and thyroid cancer. JAMA 1977; 133: 2089-2091. [CrossRef]
7. Kerber PA, Till JE, Simon SL, Lyon JL, Thomas DC, Preston-Martin S, et al. A cohort study of thyroid disease in relation to fall out from nuclear weapons. JAMA 1993; 270: 2076-2082. [CrossRef]
8. Goldgar DE, Easton DF, Cannon-Albright LA, Skolnick MH. A systemic population - based assessment of cancer risk in first degree relatives of cancer probands. J Natl Cancer Inst 1994; 86: 1600-1608. [CrossRef]
9. Sipple J. The association of pheochromocytoma with carcinoma of the thyroid gland. Am J Med 1961; 31: 163-166. [CrossRef]
10. Williams ED, Pollock DJ. Multiple mucosal neuromata with endocrine tumours: a syndrome allied to von Recklinghausen's disease. J Pathol Bacteriol 1966; 91: 71-80. [CrossRef]
11. Krampitz GW, Norton JA. The discovery of the RET proto-oncogene and its role in MEN-2 In The Supreme Triumph of the Surgeon's Art. Zeiger MA, Shen WT, Felger EA. Editors 2013 Chapter 15,p 175-193. Medical Humanities Consortium University of California.
12. Steiner AL, Goodman AD, Powers SR. Study of a kindred with pheochromocytoma, medullary thyroid carcinoma, hyperparathyroidism and Cushing's disease: multiple endocrine neoplasia, type 2. Medicine (Baltimore) 1968; 47: 371-409. [CrossRef]
13. Sizemore GW, Health H, 3rd, Carney JA. Multiple endocrine neoplasia type 2. Clin Endocrinol Metabolism 1980; 9: 299-315. [CrossRef]
14. Farndon JR, Leight GS, Dilley WG, Baylin SB, Smallridge RC, Harrison TS, et al. Familial medullary thyroid carcinoma without associated endocrinopathies: a distinct clinical eentity. Br J Surg 1986; 73: 278-281. [CrossRef]
15. Siqueira DR, Romitti M, da Rocha AP, Ceolin L, Meotti C, Estivalet A, et al. The RET polymorphic allele S836S is associated with early metastatic disease in patients with hereditary or sporadic medullary thyroid carcinoma. Endocr Relat Cancer 2010; 17: 953-963. [CrossRef]
16. Robinson D, Orr T. Carcinoma of the thyroid and other diseases of the thyroid in identical twins. AMA Arch Surg 1955; 70: 923-928. [CrossRef]
17. Sturgeon C, Clark OH. Familial nonmedullary thyroid cancer. Thyroid 2005; 15: 588-593. [CrossRef]
18. Bongarzone I, Fugazzola L, Vigneri P. Mariani L, Mondellini P. Age-related activation of the tyvrosine kinase receptor protooncogenes RET and NTREK1 in papillary thyroid carcinoma. J Clin Endocrinol Metab 1996; 81: 2006-2009. [CrossRef]
19. Grogan RH, Mitmaker EJ, Clark OH. The evolution of biomarkers in thyroid cancer –from mass screening to a personalized biosignature. Cancers 2010; 2: 885-912. [CrossRef]
20. Giordano TJ, Kuick R, Thomas DG, Misek DE, Vinco M, Sanders D, et al. Molecular classification of papillary thyroid carcinoma: distinct BRAF, RAS, RET/PTC mutation-specific gene expression profiles discovered by DNA microarray analysis. Oncogene 2005; 24: 6646-6656. [CrossRef]
21. Vasko V, Hu S, Wu G, Xing JC, Larin A, Savchenko V, et al. High prevalence and possible de novo formation of BRAF mutation in metastasized papillary thyroid cancer in lymph nodes. J Clin Endocrinol Metab 2005; 90: 5265-5269. [CrossRef]
22. Nikiforova MN, Kimura ET, Gandhi M, Biddinger PW, Knauf JA, Basolo P, et al. BRAF mutations in thyroid tumors are restricted to papillary carcinomas and anaplastic or poorly differentiated carcinomas arising from papillary carcinomas. J Clin Endocrinol Metab 2003; 88: 5399-5404. [CrossRef]
23. Xing M, Westra WH, Tufano RP, Cohen Y, Rosenbaum E, Rhoden KJ, et al. BRAF mutation predicts a poorer clinical prognosis for papillary thyroid cancer. J Clin Endocrinol Metab 2005; 90: 6373-6379. [CrossRef]
24. Nikiforova MN, Lynch RA, Biddinger PW, Alexander EK, Dom GW 2nd, Tallini G, et al. RAS point mutations and PAX 8-PPAR gamma rearrangements in thyroid tumors: evidence for distinct molecular pathways in thyroid follicular carcinoma. J Clin Endocrinol Metab 2003; 88: 2318-2322. [CrossRef]
25. Garcia-Rostan G, Zhao H, Camp RL, Pollan M, Herrero A, Pardo J, et al. Ras mutations are associated with aggressive tumor phenotypes and poor prognosis in thyroid cancer. J Clin Oncol 2003; 21: 3226-3235. [CrossRef]
26. Grieco A, Miranda C, Pierotti MA. Rearrangements of NTRK 1 gene in papillary thyroid carcinoma. Mol Cell Endocrinol 2009; 321: 44-49. [CrossRef]
27. Krol TG, Sarraf P, Pecciarini L, Chen CJ, Mueller E, Spiegelman BM, et al. PAX8-PPARgamma fusion oncogene in human thyroid carcinoma. Science 2000; 289: 1357-1360. [CrossRef]
28. Jossart GH, Epstein HD, Shaver JK, Weier HU, Greulich KM, Tezelman S, et al. Immunocytochemical detection of p53 in human thyroid carcinomas is associated with mutation and immortalization of cell lines. J Clin Endocrinol Metab 1996; 81: 3498-3504. [CrossRef]
29. Brunaud L, Zarnegar R, Wada N, Magrane G, Wong M, Duh QY, et al. Chromosomal aberrations by comparative genomic hybridization in thyroid tumors in patients with familial nonmedullary thyroid cancer. Thyroid 2003; 13: 621-629. [CrossRef]
30. Bignell GR, Canzian F, Shayeghi M, Stark M, Shugart YY, Biggs P, et al. Familial nontoxic multinodular thyroid goiter locus maps to chromosome 14q but does not account for familial nonmedullary thyroid cancer. Am J Hum Genet 1997; 61: 1123-1130. [CrossRef]
31. Canzian F, Amati P, Harach HR, Kraimps JL, Lesueur F, Barbier J, et al. A gene predisposing to familial thyroid tumors with cell oxyphilia maps to chromosome 19p13.2. Am J Hum Genet 1998; 63: 1743-1748. [CrossRef]
32. Malchoff CD, Sarfarazi M, Tendler B, Forouhar F, Whalen G, Joshi V, et al. Papillary thyroid carcinoma associated with papillary renal neoplasia: genetic linkage analysis of a distinct heritable tumor syndrome. J Clin Endocrinol Metab 2000; 85: 1758-1764. [CrossRef]
33. McKay JD, Lesueur F, Jonard L, Pastore A, Williamson J, Hoffman L, et al. Localization of a susceptibility gene for familial nonmedullary thyroid carcinoma to chromosome 2q21. Am J Hum Genet 2001; 69: 440-446. [CrossRef]
34. Harach HR. Familial nonmedullary thyroid neoplasia. Endocrine Pathology 2001; 12: 97-112. [CrossRef]
35. Mallory SB. Cowden syndrome (multiple hamartoma syndrome). Dermatol Clin 1995; 13: 27-31.
36. Ishikawa Y, Sugano H, Matsumoto T, Furuichi Y, Miller RW, Goto M. Unusual features of thyroid carcinomas in Japanese patients with Werner syndrome and possible genotype-phenotype relations to cell type and race. Cancer 1999; 85: 1345-1352. [CrossRef]
37. Yang GC, Yao JL, Feiner HD, Roses DF, Kumar A, Mulder JE. Lipid-rich follicular carcinoma of the thyroid in a patient with McCune-Albright syndrome. Mod Pathol 1999; 12: 969-973.
38. Stratakis CA, Courcoutsakis NA, Abati A, Filie A, Doppman JL, Carney JA, et al. Thyroid gland abnormalities in patients with the syndrome of spotty skin pigmentation, myxomas, endocrine overactivity, and schwannomas (Carney complex). J Clin Endocrinol Metab 1997; 82: 2037-2043. [CrossRef]
39. Jendrzejewski J, Tomsic J, Lozanski G, Labanowska J, He H, Liyanarachchi S, et al. Telomere length and telomerase reverse transcriptase gene copy number in patients with papillary thyroid carcinoma. J Clin Endocrinol Metab 2011; 96: E1876-E1880. [CrossRef]
40. Suh I, Filetti S, Vriens MR, Guerrero MA, Tumino S, Wong M, et al. Distinct loci on chromosome 1q21 and 6q22 predispose to familial nonmedullary thyroid cancer: a SNP array-based linkage analysis of 38 families. Surgery 2009; 146: 1073-1080. [CrossRef]
41. Uchino S, Noguchi S, Kawamoto H. Familial nonmedullary thyroid carcinoma characterized by multifocality and a high recurrence rate in a large study population. World J Surg 2002; 26: 897-902. [CrossRef]
42. Cavaco BM, Batista LG, Sobrinho VL. Mapping a new familial thyroid epithelial neoplasia susceptibility locus to chromosome 8p23. 1-p22 by high density single-nucleotide polymorphism genome-wide linkage analysis. J Clin Endocrinol Metab 2008; 93: 4426-4430. [CrossRef]
43. Xiong Y, Zhang L, Holloway AK, Wu X, Su L, Kebebew E. MiR-886-3p regulates cell proliferation and migration, and is dysregulat-

ed in familial non-medullary thyroid cancer. PLoS One 2011; 6: e24717. [CrossRef]
44. Capezzone M, Cantara S, Marchisotta S, Filetti S, De Santi MM, Rossi B, et al. Short telomeres, telomerase reverse transcriptase gene amplification, and increased telomerase activity in the blood of familial papillary thyroid cancer patients. J Clin Endocrinol Metab 2008; 93: 3950-3957. [CrossRef]
45. He M, Bian B, Gesuwan K. Gulati N, Zhang L, Nilubol N, et al. Telomere length is shorter in affected members of families with familial non-medullary thyroid cancer. Thyroid 2013; 23: 301-307. [CrossRef]
46. Cantara S, Pisu M, Frau DV, Caria P, Dettori T, Capezzone M, et al. Telomere abnormalities and chromosome fragility in patients affected by familial papillary thyroid cancer. J Clin Endocrinol Metab 2012; 97: E1327-31. [CrossRef]
47. Alsanea O, Wada N, Ain K, Wong M, Taylor K, Ituarte PH, et al. Is familial non-medullary thyroid carcinoma more aggressive than sporadic thyroid cancer? A multicenter series. Surgery 2000; 128: 1043-1051. [CrossRef]
48. Triponez F, Wong M, Sturgeon C, Caron N, Ginzinger DG, Segal MR, et al. Does familial non-medullary thyroid cancer adversely affect survival? World J Surg 2006; 30: 787-793. [CrossRef]
49. Mazeh H, Benavidez J, Poehls JL, Youngwirth L, Chen H, Sippel RS. In patients with thyroid cancer of follicular cell origin, a family history of nonmedullary thyroid cancer in one first-degree relative is associated with more aggressive disease. Thyroid 2012; 22: 3-8. [CrossRef]
50. Park YJ, Ahn HY, Choi HS, Kim KW, Park do J, Cho BY. The long-term outcomes of the second generation of familial nonmedullary thyroid carcinoma are more aggressive than sporadic cases. Thyroid 2012; 22: 356-362. [CrossRef]
51. Loh KC. Familial nonmedullary thyroid carcinoma: a meta-review of case series. Thyroid 1997; 7: 107-113. [CrossRef]
52. Maxwell EL, Hall FT, Freeman JL. Familial non-medullary thyroid cancer: a matched-case control study. Laryngoscope 2004; 114: 2182-2186. [CrossRef]
53. Ito Y, Kakudo K, Hirokawa M, Fukushima M, Yabuta T, Tomoda C, et al. Biological behavior and prognosis of familial papillary thyroid carcinoma. Surgery 2009; 145: 100-105. [CrossRef]
54. Robenshtok E, Tzvetov G, Grozinsky-Glasberg S, Shraga-Slutzky I, Weinstein R, Lazar L, et al. Clinical characteristics and outcome of familial nonmedullary thyroid cancer: a retrospective controlled study. Thyroid 2011; 21: 43-48. [CrossRef]
55. Moses W, Weng J, Kebebew E. Prevalence, clinic-pathologic features, and somatic genetic mutation profile in familial versus sporadic nonmedullary thyroid cancer. Thyroid 2011; 19: 1343-1349.
56. Lupoli G, Vitale G, Caraglia M, Fittipaldi MR, Abbruzzese A, Tagliaferri P, et al. Familial papillary thyroid microcarcinoma: a new clinical entity. Lancet 1999; 353: 637-639. [CrossRef]
57. Charkes ND. On the prevalence of familial non-medullary thyroid cancer in multiple affected kindreds. Thyroid 2006; 16: 181-186. [CrossRef]
58. Burgess JR, Duffield A, Wilkinson SJ, Ware R, Greenaway TM, Percival J, et al. Two families with an autosomal dominant inheritance pattern for papillary carcinoma of the thyroid. J Clin Endocrinol Metab 1997; 82: 345-348. [CrossRef]
59. Khan A, Smellie J, Harrington K, Newbold K. Familial nonmedullary thyroid cancer: a review of the genetics. Thyroid 2010; 20: 795-801. [CrossRef]
60. Vriens MR, Sabanci U, Epstein HD, Ngai S, Duh QY, Siperstein AE, et al. Reliability of fine-needle aspiration in patients with familial nonmedullary thyroid cancer. Thyroid 1999; 9: 1011-1016. [CrossRef]
61. Němec J, Soumar J, Zamrazil V, Pohunková D, Motlík K, Mirejovský P. Familial occurrence of differentiated non-medullary thyroid carcinoma. Oncology 1975; 32: 151-157. [CrossRef]