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 kadınlar arasında en sık görülen kanserler arasında altıncı sıradadır ve tiroid kanserli hastaların çoğununda sporadik hastalık mevcuttur. Bununla birlikte, medüller tiroid kanserinin yaklaşık yüzde 25’inde ve papiller tiroid kanserinin 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 tiroid kanserini hastalarının postoperatif tedavi miktarı açısından birçok tartışma vardır. Bu derleme bu ilginç konu hakkında cerrahlara bilgi vermek amacıyla hazırlanmıştır.

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

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...
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 Fambon 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 (FNMTMTC) 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 FNMTMTC 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).

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 cannot 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 members 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 FNMTMTC.

<p>| Table 1. Genetics of familial non-medullary thyroid cancer |
|---------------------------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Genetic Abnormality</th>
<th>Chromosome*</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial multinodular goiter</td>
<td>14q31</td>
<td>Bignell et al. (30)</td>
</tr>
<tr>
<td>Thyroid cancer with oxyphilia</td>
<td>19p13.2</td>
<td>Canzian et al. (31)</td>
</tr>
<tr>
<td>PTC with papillary renal neoplasia</td>
<td>1q21</td>
<td>Malchoff et al. (32)</td>
</tr>
<tr>
<td>Follicular variant of PTC</td>
<td>2q21</td>
<td>McKay et al. (33)</td>
</tr>
<tr>
<td>PTC</td>
<td>8p23.1-1p22</td>
<td>Cavaco et al. (42)</td>
</tr>
<tr>
<td>PTC</td>
<td>1q21&amp;6q22</td>
<td>Suh et al. (40)</td>
</tr>
</tbody>
</table>

Table 1. Genetics of familial non-medullary thyroid cancer

<p>| Table 2. Genetics and inheritance in familial syndromes with non-medullary thyroid cancer |
|---------------------------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Chromosome</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial adenomatous polypsis</td>
<td>APC</td>
<td>5q21</td>
<td>AD</td>
</tr>
<tr>
<td>Cowden’s disease</td>
<td>PTEN</td>
<td>10q22-23</td>
<td>AD</td>
</tr>
<tr>
<td>Werner’s syndrome (in Japanese)</td>
<td>WRN</td>
<td>8p11-21</td>
<td>AR</td>
</tr>
<tr>
<td>Carney’s complex</td>
<td>PRKAR1a</td>
<td>17q24</td>
<td>AD</td>
</tr>
<tr>
<td>McCune-Albright syndrome</td>
<td>GNAS1</td>
<td>20q13.1-13.2</td>
<td>Mosa (10)</td>
</tr>
</tbody>
</table>

AD: autosomal dominant; AR: autosomal recessive
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. FNMC 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 polygenic 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.
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66