Familial Differentiated Carcinoma of the Thyroid

3

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3.1 Introduction

In most series, thyroid cancers arising from follicular cells account for about 90% of malignant tumors of the thyroid [1–3]. The remainder are medullary cancers, which arise from parafollicular cells, lymphomas, sarcomas, and metastatic cancers. A proportion of medullary cancers are unequivocally recognized to be hereditary. These include medullary cancers occurring as part of the syndromes of multiple endocrine neoplastic syndromes MEN 2A and MEN 2B (MEN 3) and some isolated cases of medullary cancer [4]. These are discussed separately in Chap. 20. The genetics have been defined as autosomal dominant, and the cause of MEN 2A and familial medullary cancer is a mutation in the c-ret proto-oncogene [5–8].

Differentiated or nonmedullary cancers of the follicular epithelium are usually considered to be sporadic and nonfamilial. There is a growing body of evidence that some cases are familial. In my clinic about 2% of patients have a first-degree relative with similar disease. Some report an incidence of 4–5% [9, 10]. The first report was in identical twins and was published in 1955 [11]. There are now several reports of familial cases, including several from this institute [12–29]. Some investigators consider that familial thyroid cancers are more aggressive than the sporadic cases [9, 30]. This chapter will review the published reports and as far as possible analyze whether the natural history of the disease is different from the sporadic variety. The mode of inheritance and genetic susceptibility, including the relationship with Cowden's, Gardner's, and other syndromes are discussed. The molecular genetics will be reviewed. Advice about management of the patients and their families is included.

3.2 Etiology of Nonmedullary Thyroid Cancers

In most patients with differentiated thyroid cancer arising from thyroid follicular cells, there is no single causal factor which can be blamed for producing the cancer. However, there is abundant evidence that external radiation is an important cause, in particular when the patients are young at the time of exposure [31–34]. This has been shown in epidemiological studies of patients who had

neck and chest radiation for benign or malignant disorders. The association has been documented for radiation to the scalp in the treatment of ringworm. These patients were exposed to doses as low as 10 rad (10 cGy) [35]. Doses of several hundred radians (100 rad = 1 Gy), prescribed to treat "status lymphaticus" and acne, caused thyroid cancer in about 5–10% of patients. Therapeutic doses of 4,000 rad (40 Gy) for Hodgkin's disease produced a 20-fold increase in thyroid cancer [36]. Currently we have identified 12 patients with thyroid cancer out of more than 1,800 patients with Hodgkin's disease who received therapeutic neck irradiation. In every report the increase in cancers was of the papillary type [26]. The data that radiation is an etiological factor, although compelling, begs the question: Why do so few patients exposed develop clinical disease? What puts some patients at risk and protects others? In evaluating familial thyroid cancers, it is important to review prior history to exclude external radiation. This brings into discussion the role of genetics. Cancers are due to a change in DNA, which results in a clone of cells having the potential to divide faster, to invade surrounding tissues, and to metastasize. This can be due to promoters of these characteristics, called "oncogenes." Alternatively there can be loss of the protective mechanisms which continually repair breaks in DNA or which suppress those characteristics of malignancy, suppressor genes. Radiation has been shown to alter both of these mechanisms.

This interplay of familial and cancerogenic factors is seen clinically. In one of the families, we reported two brothers with thyroid cancer who both had been irradiated in childhood over the neck and face, for acne [27]. One has had minimal disease, the other died from aggressive cancer that was unresponsive to all therapies. There are other similar reports [37, 38]. Were these cancers due to radiation, or familial, or both? Did the radiation cause undifferentiated disease in some but not others?

In contrast, it has generally been accepted that internal radiation from radionuclides of iodine used diagnostically or therapeutically is not associated with an increase in thyroid cancer. There are large studies showing that patients treated with radio-iodine for hyperthyroidism do not have an increase in thyroid cancers [39]. However, the dramatic increase in thyroid cancer in children

Table 3.1. Relationship of familial nonmedullary cancers with goiter and nodular goiter

Reference	Cancers *(n)*	Goiters *(n)*	Familiy members *(n)*
Burgess et al.: family 1 [15]	7	17	25
Kraimps et al.: family 1 [29]	3	4	13
Kraimps et al.: families 2, 4, and 6 combined	6	6	19
Lote et al.: family 1 [23]	7	2	42
Lote et al.: family 2	4	2	23
Osaki et al. [17]	2 (possibly 3)	2	29

exposed to radio-iodines released from the Chernobyl nuclear power plant disaster has caused this view to be reconsidered [40–44].

The incidence of differentiated thyroid cancer varies considerably among ethnic groups. The highest incidence is in populations from the Pacific rim, in particular Filipinos. In contrast, African Americans have about one-tenth the incidence of differentiated cancers. Are some ethnic groups at a higher genetic or environmental risk for cancer than others or is there an alternative explanation? One factor that appears to increase the incidence of papillary cancer is a high dietary intake of iodine. A large study of patients with papillary cancer from several ethnic backgrounds has shown some relation to dietary iodine [45]. In contrast the incidence of follicular cancer is increased in areas of iodine deficiency where nodular goiter is endemic [46, 47]. Preexisting thyroid conditions such as goiter and nodules are associated with an increased incidence of thyroid cancer. It is clear that, in some of the families with several cases of thyroid cancer, there is also a significant proportion of patients with nodules, goiter, and multinodular goiter (Table 3.1) [15]. This raises the suspicion of a growth stimulus which, in the appropriate setting, develops malignant potential. Most patients with thyroid cancer are clinically and biochemically euthyroid, therefore thyroid-stimulating hormone and thyroid-stimulating immunoglobulins are unlikely to be involved as the cause.

3.3 Could "Familial" Thyroid Cancers be a Chance Finding?

The first question to answer is whether familial cases of differentiated thyroid cancer are chance findings. Most of the published reports indicate that between 3 and 6% of patients with differentiated thyroid cancer report a first-degree relative with the same condition. Kraimps et al. [13] found that the familial incidence was 10.5% when they studied the families of 105 consecutive patients [20]. In seven families they found 15 cases. Pal et al. compared the incidence of thyroid cancer in relatives of 339 patients with differentiated thyroid cancer to that in families of 319 matched controls. They determined that there was a 10.3-fold increase (95% confidence interval 2.2–47.6) [48]. Similarly, in an analysis of 1025 patients with thyroid cancer and 5457 first-degree relatives in Norway, there was a 5.2 times increase in men and 4.9 times increase in women [49]. From a simplistic point of view, let us use data from the USA, where 19,000 new cases of thyroid cancer are diagnosed annually from a population of 250,000,000 people. If we assume that 15,000 of the cancers are differentiated and the entire population lives to be 80 years of age, the probability that a person will be diagnosed with thyroid cancer during their lifetime is 0.48%. Charkes [34], using more sophisticated mathematics, which incorporated data from the Surveillance, Epidemiology and End Results (SEER), calculated an overall risk of 0.324%, with the risk in women of 0.459% and men of 0.189% [50]. These lifetime risks are not greatly different from our simplistic calculation. From these data, the risk of two relatives having differentiated thyroid cancer would be from 0.1–0.23% (0.324×0.324% or 0.48%×0.48%). However, the

size of the family and hence number of persons at risk have to be considered. Charkes, using Poisson statistics, has calculated that the risk of two cases in one family with 12 first-degree relatives is 1.9% ± 0.2%. The probability of three or more cases is less than 0.1%. Houlston [35, 36] has estimated that a family with three members with differentiated thyroid cancer would be found by chance in 100 years but does not specify whether this would be in the UK or USA [51, 52]. Malchoff et al. [37] state that the chance of finding five members with papillary cancer to be 1 in 2 billion [53].

Ron et al. [38] have found a 5.2-fold increase in thyroid cancer in relatives of an index patient with differentiated thyroid cancer [54]. Stoffer et al. [19] have determined there is a similar (4.71-fold) increase in risk in members of 222 families with an index patient [25]. These data indicate that chance is unlikely to be the cause of finding three or more members of a family with thyroid cancer.

One factor which could actually reduce the familial association is that patients may not know their relatives have thyroid cancer. In some countries physicians are reluctant to discuss the diagnosis of cancer with patients, and thyroid surgery might not be thought to be for cancer. This understanding can be strengthened by the excellent prognosis in most patients with differentiated thyroid cancer.

3.4 Genetics and Associated Syndromes

There is a definite relationship between thyroid cancer and familial adenomatous polyposis (FAP) and Gardner's syndrome [55, 56], which is the association of FAP with soft tissue tumors, osteomas, and miscellaneous neoplasms [5, 57–62]. Houlston has estimated that less than 0.1% of differentiated thyroid cancers have this association [52]. He has determined that the same percentage have the combination of differentiated thyroid cancer and Cowden's syndrome. Patients with Cowden's syndrome have nodular goiters, multiple hamartomas, skeletal abnormalities, and a 50% risk of breast cancer [63, 64]. Thyroid cancer has been described in patients with Peutz-Jeghers syndrome [51] and ataxia-telangiectasia [65]. We have also found differentiated thyroid cancer in three patients with osteogenic sarcoma [66]. Some investigators exclude patients who have differentiated thyroid cancer and FAP, or Gardner's, or Cowden's syndrome from the classification of familial nonmedullary thyroid cancer. This is not logical, because the associated disorders are also familial and the combination could be more etiologically informative.

In most of the publications of families with first-degree relatives with differentiated thyroid cancer, there are only two patients, e.g. two sisters, two brothers, one brother and one sister, mother and child, father and child, and it is not possible to assign a specific pattern of inheritance. Several population-based studies and meta-analysis of these reports also fail to answer the mode of inheritance [54, 67–71]. There are a few reports of families in which several members are affected. Table 3.2 lists families in which three or more members have thyroid cancer. Lote et al. have described two kindreds with seven and

four patients [23]. Burgess et al. have also described two families with multiple patients with papillary cancer [15]. In one family of 25 individuals, 7 patients had proven thyroid cancer and 2 others probably had cancer. Nine additional members had multinodular goiter. In the second family, identical twin brothers had papillary cancer and each had a daughter who was found to have this type of cancer. They felt that the inheritance was autosomal dominant. We have con-

Table 3.2. Families with three or more differentiated thyroid cancers

Reference	Index patient	Thyroid cancers *(n)*	Family members *(n)*	Generations studied *(n)*	Relationship
Lote et al.: pedigree 1 [23]	Woman	7	51	3	2 daughters Female cousin 2 nieces, 1 nephew
Lote et al.: pedigree 2	Woman	4	33	3	Maternal aunt 2 sons
Phade et al. [24]	12-year-old boy	3	Not discussed	Same generation	Two sisters
Stoffer et al.: family B [25]	Male	5	23	4	2 cousins Aunt Great uncle
Stoffer et al.: family D	Woman	3	27	4	Mother Uncle
Stoffer et al.: family G	29-year-old woman	4	24	5	Sister Mother Maternal uncle
Malchoff et al. [53]	26-year-old woman	5	30	4	Sister 1 daughter, 1 son 1 great-niece
Burgess et al.: kindred 1 [15]	62-year-old woman	7	25	4	4 children 2 relaives (cousin and niece) 2 additional cases
Burgess et al.: kindred 2	49-year-old man	4	12	3	Twin brother Daughters of patient and twin
Kraimps et al.: kindred 1 [29]	10-year-old boy	3	13	3	11-year-old niece 27-year-old nephew
Ozaki et al.: family 8 [17]	40-year-old man	3	29	4	27-year-old sister 37-year-old brother

sulted on one member of a family with five patients over three generations with thyroid cancer, whose genetic transmission appears to be dominant.

3.4.1 Molecular Genetics of Familial Thyroid Cancer

Although most cases of nonmedullary thyroid cancer are sporadic, there is increasing evidence of a familial form. There is considerable interest in identifying a gene or genes that cause susceptibility (see Table 3.3). There is some evidence that nonmedullary thyroid cancer is autosomal dominant with partial penetrance and is not associated with other malignancies. Specific genes responsible for susceptibility to familial nonmedullary thyroid cancer without an associated comorbidity have not yet been identified [72]. Several groups of investigators are studying the molecular genetics of familial nonmedullary cancer. If a single lesion could be identified, it would allow screening of families to identify those at risk and counsel them on management. It could possibly at some future date lead to novel gene therapies.

Bignell et al. have found a gene on chromosome 14q32 which they call *MNG 1*, because members of the family studied had multinodular goiter and familial thyroid cancer [73]. In a second family, there is a gene designated *TCO* on chromosome 19q13.2, which predisposes to multinodular goiter and cancer [74]. In an analysis of 60 small families, there is no relation to *MNG 1*, *TCO*, or *RET* [75]. McKay et al. have found that *MNG 1* and *TCO* are not causal in their Tasmanian family [76]. McKay et al. in a multinational collaboration have shown a susceptibility locus on 2q21 [77].

The gene for the TSH receptor is on chromosome 14q but it has been shown to be distinct from *MNG 1* and has not been implicated in the cause of thyroid cancer [78]. Mutations of the TSH receptor gene can produce hyperfunctioning nodules, but these are almost never malignant. Mutations of this gene have also caused a hyperthyroidism in newborn. Bevan et al. have attempted to find mutations in 22 families with nonmedullary thyroid cancer [10]. They have found no evidence for MNG1, fPTC, PTEN, TSHR or TRK and their work supports the hypothesis that this condition is not homogeneous.

Rearranged forms of the RET proto-oncogene have been identified as the susceptibility genes for development of sporadic forms of papillary thyroid cancer. The RET proto-oncogene is located on chromosome 10q11.2 and encodes a transmembrane receptor of the tyrosine kinase family. *RET/PTC1*, *RET/PTC/2*, and *RET/PTC3* are chimeric oncogenes formed from the rearrangement of the RET proto-oncogene. They have been identified as one genetic event leading to the development of sporadic cases of nonmedullary thyroid cancer [79, 80]. Rearrangement of the RET proto-oncogene has also been identified in children who developed papillary cancer after exposure to radioactive iodine released during the Chernobyl reactor accident [81, 82]. In the majority of these cases, induction of papillary thyroid cancer was a consequence of *RET/PTC1* rearrangements [83]. In other cases, rearrangement of the *NTRK1* gene located on chromosome 1q22 was found to be the responsible gene. TRK family receptor

genes are also known to participate in development of medullary thyroid cancer [64].

Papillary thyroid cancer is known to overexpress c-met located on 7q31. In contrast, inactivation of this gene has been shown to be significant in the development of follicular as well as anaplastic thyroid cancer. Loss of heterozygosity on chromosomes 10q, 3p, and 17p appears to be more common in follicular cancer than papillary cancer. In fact, it has been shown that papillary cancer has exceedingly low rates of loss of allelic heterozygosity [84–86].

Cowden's syndrome is an autosomal dominant disorder characterized by increased risk of thyroid cancer in combination with development of hamartomas and increased risk of development of breast tumors. The loss of a tumor suppressor gene has been found to be responsible for susceptibility to this syndrome. Deletion mapping by examination of loss of heterozygosity of polymorphic markers was employed to ascertain the fine structure of a region of chromosome 10 [87]. Using this technique, the tumor suppressor gene whose deletion is responsible for Cowden's syndrome was identified as the *PTEN* tumor suppressor gene located on 10q23.3 [88, 89]. *PTEN* encodes for a phosphatase important in the phosphatidylinositol 3-kinase signal conduction pathway. Inactivation of *PTEN* tumor suppressor gene has also been implicated in several cases of sporadic follicular thyroid tumors [90].

Familial adenomatous polyposis is an inherited autosomal dominant tumor syndrome characterized by colonic polyps with eventual malignant transformation. It is caused by germ-line mutations of the *APC* gene, which has been

Table 3.3. Genes reported to be associated with familial nonmedullary thyroid cancer

Entity	Gene	Chromosome
Nonmedullary cancer, familial	*MNG1*, *TCO*, *RET*, *TRK*, *MET*, *TSHR*, *APC*, *PTEN* have been excluded	?
Papillary cancer, sporadic	*RET/PTC1*, *RET/PTC2*, *RET/PTC3*	10q
Papillary cancer, Chernobyl	*RET/PTC1* (common) *NTRK1* rearrangement (rare)	10q 1q22
Follicular cancer, sporadic		
Familial multinodular goiter	*MNG1*	14q32
Nonmedullary thyroid cancer associated with multinodular goiter	*TCO*	19q13.2
Familial adenomatous polyposis & Gardner's syndrome	*APC*	5q21
Cowden's syndrome	*PTEN*	10q23
Thyrotropin receptor	*TSHR*	
Familial medullary thyroid cancer (men)	*RET*	10q11.2

mapped to chromosome 5q21. Malchoff et al. have studied 18 family members with both familial polyposis coli and papillary cancer [53]. They conclude that the two conditions are not caused by the same genetic abnormality. The association between nonmedullary thyroid cancer and this familial tumor syndrome is well known. Investigators have used linkage analysis, employing polymorphic markers located close to the *APC* gene, to determine whether familial papillary thyroid cancer is related to loss of the *APC* gene. It has been concluded that familial papillary thyroid cancer is genetically distinct from familial adenomatous polyposis. Gardner's syndrome is similar to familial adenomatous polyposis coli in inheritance pattern, association with papillary thyroid cancer, development of adenomas in the colon, and risk of carcinoma. Gardner's syndrome differs from polyposis coli in the addition of adenomatous polyps located in the small intestine and presence of extraintestinal lesions such as osteomas, skin fibromas, and epidermal cysts. In investigations evaluating the genetic linkage of papillary thyroid cancer, patients with Gardner's syndrome have been grouped together with patients with familial adenomatous polyposis coli; no separate investigations have been published to date [91–93].

MTS-1 encodes the tumor suppressor gene p16 and MTS-2 encodes the tumor suppressor gene p15. Structural changes in these genes have been associated with various cancers. Several investigators have concluded that deletion of MTS-1 and MTS-2 are not associated with development of thyroid cancers. However, base-pair exchange at these sites was found to contribute to development of tumor. Loss of p16 has been associated with transformation from well-differentiated thyroid cancer to anaplastic cancer [94, 95].

3.4.2 Natural History of Familial Thyroid Cancer

There is evidence that the ratio of men to women with familial thyroid cancer is nearer to unity than in sporadic cases where the ratio is about 1:3 [9]. There is conflicting data on whether familial differentiated thyroid cancer is more often multifocal, more advanced and aggressive, and has a worse prognosis than the sporadic variety [9, 28, 69, 96]. An alternative explanation is that the patients are younger, and it is accepted that, in young patients with papillary cancer, the lesions are larger, they are more likely to be multifocal, and more frequently associated with lymph node and pulmonary metastases. The younger age of patients with familial cancer could be due to increased interest in the relatives of an index case.

Recurrences of familial thyroid cancer are thought to be more common and the mortality greater. Takami et al. found that 82% had cervical metastases [30], which is an average of 65 nodes containing metastases in 61 patients subjected to modified neck dissection. Six had pulmonary metastases at presentation, 31% had a recurrence, and 5 patients died from their disease. Lote et al. found a statistically significant increased incidence in lymph node metastases compared with nonfamilial controls [23]. The average age of the patients was 37.6 years which, although similar to most series in the USA, was younger than

the 52.8 years of their controls. Grossman et al. treated 14 patients, 13 of whom had multifocal disease, 57% had cervical node metastases, and 50% recurred [27]. The mean age was 40 years, and the male to female ratio 1:1.3. Uchino et al. reported on 154 families with two or more thyroid cancers from a denominator of 6,458 patients [9]. There was a higher incidence of multifocality (42% vs 30%), recurrence (16.3% vs 9.6%), and disease-free survival in the familial cases. The survival was the same in familial versus sporadic cases. It is hard to argue with data from such large numbers of patients.

Stoffer et al. found that 18 of 22 patients had multifocal disease, 5 (23%) had cervical nodal metastases, and 1 had a pulmonary metastasis [25]. They found the average age of the patients, 37.8 years, was not different from their sporadic cases. We described five pairs of sibs and have now treated 19 patients who have a first-degree relative. In general the prognosis and natural history appears similar to sporadic nonmedullary thyroid cancer. One of the male sibs developed a skeletal metastasis and died, but he had been exposed to radiation, and the familial designation as the sole cause of his cancer is questionable. The remainder of the patients who have been treated and followed at Stanford have had a good outcome.

3.5 Clinical Implications of Familial Nonmedullary Thyroid Cancer

3.5.1 Primary Treatment

The fundamentals of treatment should be no different from those for sporadic cancers. When the diagnosis is made, total or near total thyroidectomy should be undertaken. In many patients whole-body scan with ^{131}I should be conducted after surgery and abnormal uptake treated with ^{131}I. The details of these treatments are described elsewhere in this book. Because of concern that familial cancers can be more aggressive, lesser surgical procedures are not recommended. Serum thyroglobulin (Tg) measurement has the same importance in follow-up of familial thyroid cancer.

3.5.2 Screening of Families

With increasing acceptance that there are familial cases of thyroid cancer, physicians should take a careful family history before concluding a cancer is sporadic. When two patients in a family are identified with thyroid cancer, this knowledge should be disseminated through the family and, when each member next consults their physician, a careful examination of the thyroid should be conducted. Since most of the families reported have only two affected members, this is sufficient. Because the prognosis in differentiated thyroid cancer

is good, the need for aggressive screening of families does not have the importance it does for medullary cancer. At the time of writing, there is no genetic or biochemical test which is of value. Any member with a nodule should have this examined by fine-needle aspiration (FNA) and all patients with suspicious and microfollicular lesions referred for thyroidectomy. When there are three or more family members with cancer, clinical screening should be more actively undertaken. In the rare families with several affected individuals in whom the cancers appear to be more aggressive, it would be reasonable to obtain ultrasound examinations and obtain an ultrasound-guided FNA of nodules more than 1 cm in diameter.

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