Familial non-medullary thyroid carcinoma displays the features of clinical anticipation suggestive of a distinct biological entity

M Capezzone, S Marchisotta, S Cantara, G Busonero, L Brilli, K Pazaitou-Panayiotou[1], A F Carli[2], G Caruso[3], P Toti[4], S Capitani[5], A Pammolli[5] and F Pacini

Section of Endocrinology and Metabolism, Department of Internal Medicine, Endocrinology and Metabolism and Biochemistry, University of Siena, Policlinico Santa Maria alle Scotte, Viale Bracci 1, 53100 Siena, Italy
[1]Department of Endocrinology-Endocrine Oncology, Theageniu Cancer Hospital, Thessaloniki, Greece
[2]Section of Endocrine Surgery, Department of Surgical Science, University of Siena, Siena, Italy
[3]Unit of Otorinolaringoiatry, University of Siena, Siena, Italy
[4]Department of Human Pathology and Oncology, University of Siena, Siena, Italy
[5]Biology Section, Department of Surgery, University of Siena, Siena, Italy

(Correspondence should be addressed to F Pacini; Email: pacini8@unisi.it)

Abstract

Non-medullary thyroid carcinoma (NMTC) is mostly sporadic, but familial clustering is described. We aimed to compare the features of patients with sporadic and familial NMTC (FNMTC) patients and to assess whether FNMTC patients with parent–child relationship exhibit the '*anticipation*' phenomenon (earlier age at disease onset and increased severity in successive generations). Among 300 NMTCs followed in the Section of Endocrinology (University of Siena, Italy), 34 (11.3%) patients, all with the papillary histotype, (16 kindred), met the criteria of FNMTC. Twenty-seven of them (79.4%) exhibited a parent–child relationship and seven (20.6%) a sibling relationship. These patients were compared with 235 patients with sporadic papillary thyroid cancer (PTCs). To analyze the features of FNMTC of the first and second generations, we cumulated the series of Siena with 32 additional FNMTC patients (15 kindred) from the Department of Endocrinology-Endocrine Oncology, Thessaloniki, Greece. Significant difference between sporadic PTC and FNMTC patients included more frequent tumor multifocality ($P=0.001$) and worse final outcome in FNMTC patients ($P=0.001$). Among 47 FNMTC with parent–child relationship, we found an earlier age at disease presentation ($P<0.0001$), diagnosis ($P<0.0001$), and disease onset ($P=0.04$) in the second generation when compared with the first generation. Patients in the second generation were more frequently males ($P=0.02$); their tumors were more frequently multifocal ($P=0.003$) and bilateral ($P=0.01$), had higher rate of lymph node metastases at surgery ($P=0.02$) and worse outcome ($P=0.04$) when compared with the first generation. In conclusion, FNMTC displays the features of clinical 'anticipation' with the second generation acquiring the disease at an earlier age and having more advanced disease at presentation.

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Introduction

Non-medullary thyroid cancer (NMTC) of the follicular thyroid epithelium accounts for nearly 80% of all thyroid cancers and it is mainly represented by the papillary histotype (papillary thyroid cancer; PTC), mostly sporadic in nature (Hay *et al*. 2002). Nevertheless, the recurrence of NMTC, in more than one subject of the same family has been described (Stoffer *et al*. 1986, Loh 1997, Hemminki & Li 2003). Cohort-based studies (Goldgar *et al*. 1994, Frich *et al*. 2001, Pal *et al*. 2001) have shown that the risk of developing NMTC is significantly greater (between 3 and 9 fold) in first-degree relatives of subjects with NMTC. While some studies reported no difference regarding outcome and survival of familial NMTC (FNMTC) patients and their sporadic counterpart (Loh 1997, Maxwell *et al*. 2004), recent studies (Grossman *et al*. 1995, Alsanea *et al*. 2000, Uchino *et al*. 2002, Triponez *et al*. 2006) have demonstrated that with

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respect to sporadic NMTCs, FNMTCs are more frequently multifocal, have higher rate of relapse, and are diagnosed at younger ages.

In this study, we demonstrate that in a series of NMTC including patients with FNMTC, the latter exhibit more aggressive tumor phenotype. In addition, when comparing the first and the second generation of FNMTC patients (47 cases), we observed that offsprings show an earlier age at disease onset and have more aggressive disease when compared with their parents. These features might recall the presence of 'genetic anticipation', the phenomenon defined as the occurrence of a genetic disorder at progressively earlier ages and with increased severity in successive generations (McInnis 1996), and suggest that FNMTC is a true familial disease rather than the fortuitous association of the same disease in a family.

Patients and methods

Our study analyzed two different issues: i) the comparison of clinical and pathological features of sporadic and familial NMTC and ii) the comparison of the first and the second generation of FNMTC with parent–child relationship.

For the first part, we retrospectively reviewed, after informed consent obtained in accordance with the local ethical committee guidelines, the clinical records of all NMTC patients ($n=300$) followed in the Section of Endocrinology of University of Siena (Italy) from 1978 to 2007. There were 230 females and 70 males, ratio F/M is 3/1, ranging 8–84 years. Final histology was PTC in 269 (89.7%) and follicular thyroid cancer (FTC) or Hürthle cell cancer in 31 (10.3%). Initial treatment (near-total thyroidectomy and ^{131}I remnant ablation) and follow-up strategy were the same in all of them. Mean follow-up was 57.7 ± 48.8 months (range 12–368 months). FNMTC was found in 34/300 (11.3%) patients belonging to 16 kindred. In the agreement with other authors (Musholt *et al*. 2000, Alsanea *et al*. 2000, Uchino *et al*. 2002, Sturgeon & Clark 2005), we defined as FNMTC the presence of two or more first-degree relatives with thyroid cancer of follicular cell origin after excluding clinical or pathological evidence of hereditary syndromes associated with NMTC, such as familial adenomatous polyposis, Gardner syndrome, Peutz–Jegher syndrome, Cowden disease. We analyzed the clinical–pathological features of familial and sporadic NMTC patients, including gender, age at diagnosis, tumor diameter, extension of the disease at diagnosis, histology, intrathyroidal dissemination of the tumor (multicentricity and bilaterality), rate of lymph node metastases, presence of other cancers, and recurrence and final status at the end of follow-up. Since all FNMTC patients had PTC, their comparison was limited to the 235 sporadic PTCs excluding patients with FTC and Hürthle cell tumors. According to standard criteria and recent guidelines (Cooper *et al*. 2006, Pacini *et al*. 2006), we define 'cured or free of disease' patients with undetectable stimulated serum Tg levels (<1.0 ng/ml), negative TgAb, and no evidence of disease (at clinical examination, neck ultrasound, negative diagnostic 131-I whole body scan, and/or other imaging techniques), whereas patients with detectable basal or stimulated serum Tg and/or evidence of disease were classified as having persistent/recurrent disease.

For the second part of the study, we pooled the 34 FNMTC patients of the Italian series (16 kindred) and 32 additional FNMTC patients (15 kindred) derived from the series of the Department of Endocrinology of the University of Thessaloniky (Greece). In total, we had 66 FNMTC patients belonging to 31 kindred.

Statistical analysis

Statistical analysis was conducted with StatView for Windows, ver.5.00.1 (SAS Institute, Cary, NC, USA). All data are presented as mean$\pm$S.D. and medians when appropriate. To compare the statistical differences between the variables of two independent groups where the condition of normality is not satisfied, the Mann–Whitney U test was used. To assess the association among qualitative variables, the Fisher's exact test was used if the expected frequencies were less than 5, otherwise the χ^2 test was performed. The age-dependent cumulative hazard of FNMTC diagnosis in the first and the second generation was calculated by Nelson–Aalen estimate and statistical comparison was made by log-rank test. Two-sides $P<0.05$ was considered significant.

To evaluate the presence of anticipation and avoid the 'insufficient follow-up time bias,' a specific procedure was created using the program Matlab (ver.6.5). In order to take this potential bias into account, we analyzed differences in age at disease manifestation, age at diagnosis, year of disease manifestation, year at diagnosis of parents, and offsprings with adjustment for a possible inadequate follow-up time (Age at Onset, AOA test) as described in details by Vieland & Huang (1998). The concept of 'age at disease onset anticipation (AOA)' is the tendency for children to develop clinical disease at an earlier age than the affected parents. The AOA test is based on the correct, bivariate right-truncated, age-at-onset distribution and has been validated as the one able to avoid the above-mentioned bias. After the age correction at the diagnosis, for the different

risk period, we applied the Z_{AO} test not to evaluate random effects but to determine the real difference between the age at onset of parents and offsprings.

Results

Comparison of FNMTC and sporadic PTC patients of the Italian series

The clinical–pathological features of FNMTC ($n=34$) and sporadic PTC patients ($n=235$) are shown in Table 1. Tumors of FNMTC patients were more frequently multifocal ($P=0.001$), tended to have higher recurrence rate ($P=0.05$), and had worse outcome ($P=0.001$) when compared with sporadic PTC patients. No difference was found regarding gender, age, primary tumor diameter, bilaterality, tumor extension, lymph node metastases, and length of follow-up and history of other malignancy. Only 2 of 34 patients affected by FNMTC showed another type of cancer: one had breast cancer with age at onset of 64 years and another had lymphoma with age at onset of 6 years, (1 and 8 years of age before the diagnosis of PTC respectively). No other known thyroid cancer-associated syndromes was present clinically in FNMTC patients.

Table 1 Demographic and disease characteristics of sporadic PTC and FNMTC patients (Italian cohort)

Parameters	FNMTC ($n=34$)	Sporadic PTC ($n=235$)	*P*
Gender: *n* (%)			0.6[a]
Male	9 (26.5)	54 (22.9)	
Female	25 (73.5)	181 (77.1)	
Age at diagnosis (years)			0.9[b]
Mean ± S.D.	47.9 + 18.2	47.5 + 16.6	
Range	14–78	14–84	
Median	44.5	48	
Tumor diameter (mm)			0.4[b]
Mean ± S.D.	17.0 + 12.5	18.3 + 11.3	
Median	15	15	
Multicentricity: *n* (%)			0.001[a]
Yes	15 (44.1)	46 (19.6)	
No	19 (55.9)	189 (80.4)	
Bilaterality: *n* (%)			0.4[a]
Yes	10 (29.4)	55 (23.4)	
No	24 (70.6)	180 (76.6)	
Tumor extention: *n* (%)			0.2[a]
Intrathyroidal	22 (64.7)	176 (74.9)	
Extrathyroidal	12 (35.3)	59 (25.1)	
Metastases: *n* (%)			0.9[a]
Yes	10 (29.4)	69 (29.3)	
No	24 (70.6)	166 (70.7)	
Outcome: *n* (%)			0.001[a]
Cured	23 (67.6)	206 (87.7)	
Not cured	9 (26.5)	28 (11.9)	
Tumor-related death	2 (5.9)	1 (0.4)	
Recurrences: *n* (%)			0.05[c]
Yes	4 (11.8)	8 (3.4)	
No	30 (88.2)	227 (96.6)	
Other cancers: *n* (%)			0.7[c]
Yes	2 (5.9)	12 (5.1)	
No	32 (94.1)	223 (94.9)	
Follow-up (months)	50.8 + 32.2	55.8 + 45.1	0.5[b]

[a]By χ^2 test.
[b]By Mann–Whitney *U* test.
[c]Fisher's exact test.

Comparison of FNMTC patients in the first and second generation

Cumulating the Italian and the Greek series (31 pedigrees, 66 FNMTC patients, and all PTC), FNMTC recurred in two family members in 28 pedigrees, in three family members in 2 pedigrees, and in four members in 1 pedigree. A parent–child relationship was found in 22 kindred (47 family members) and a sibling relationship was found in 9 kindred (19 members). The two pedigrees with three affected family members had both parent–child and sibling relationships: one family had one parent and two offsprings affected, the other had two sisters and one of theirs offspring affected. The single pedigree with four family members had one parent and three offsprings affected. To compare the clinical–pathological features of FNMTC patients with parent–child relationship, we excluded the nine kindred with a sibling relationship.

The diagnosis of PTC was made firstly in the first generation in 17/22 (77.3%) kindred. The time interval between the diagnosis in the propositus and in the second familial member ranged between 1 and 20 years with a mean of 4.5 years. As shown in Fig. 1, age at diagnosis was always younger in the second generation

Figure 1 Intrapair difference in age at diagnosis in parent–offspring pairs (22 kindred) of FNMTC (age at diagnosis of the offspring minus age at diagnosis of the corresponding parent). Each bar represents a parent–offspring pair (*same kindred and **same kindred).

Table 2 Age at presentation, at diagnosis and at disease onset in FNMTC (both Italian and Greek cohorts) of the first and second generations, respectively

Parameters	First generation ($n=22$)	Second generation ($n=25$)	*P*
Age at disease presentation (years)			<0.0001[a]
Mean ± S.D.	54.6 + 14.7	29.8 + 11.1	
Range	20–75	14–53	
Median	57.5	31	
Age at diagnosis (years)			<0.0001[a]
Mean ± S.D.	60.3 + 10.6	31.8 + 11.6	
Range	37–75	14–56	
Median	62.5	32	
Age at disease onset (years)			$=0.0347$[b]
Mean ± S.D.	71.7 + 12.7	44.4 + 8.3	

[a]By Mann–Whitney *U* test.
[b]By AOA test.

when compared with the first generation with a mean negative difference of -29.3 ± 7.9 years and a range of $-12/-43$ years.

As shown in Table 2, mean age at presentation and at diagnosis were significantly ($P<0.0001$) younger in the second generation. To rule out that this phenomenon may be due to a screening effect (members of the second generation may be screened for thyroid cancer after a member of the first generation has been diagnosed with thyroid cancer), we applied the AOA test. Using this test and assuming different variances ($\sigma_1^2 \neq \sigma_2^2$), the estimated mean age at onset of the disease in the first generation was 71.7 ± 12.7 years, significantly older (Z_{AO} test $=1.8159$, $P=0.0347$) than the estimated mean age at onset of the offsprings (44.4 ± 8.3 years). Applying the Nelson–Aalen method (Fig. 2), the age-dependent cumulative hazard of FNMTC diagnosis in patients of the second generation was significantly higher than in those

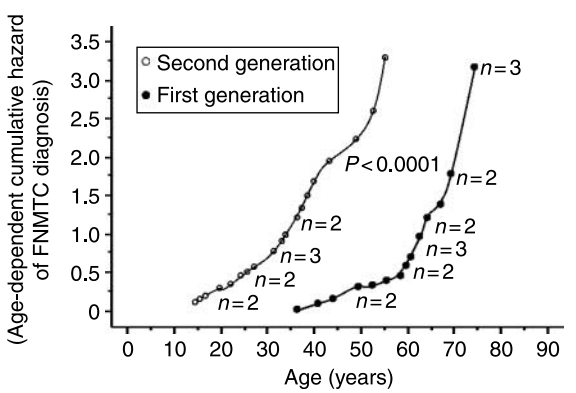

Figure 2 Age-dependent hazard of FNMTC diagnosis in the second (open circles) and the first (close circles) generations (by Nelson–Aalen plot. $P<0.0001$ by log-rank test).

of the first generation ($P<0.001$). In addition, as shown in Table 3, patients of the second generation had a higher rate of local or distant metastases ($P=0.02$), tumor multicentricity ($P=0.003$), and bilaterality ($P=0.01$) at the time of diagnosis and a worse outcome ($P=0.04$) at final follow-up when compared with their parents. These findings and that of younger age at disease onset in the second generation confirm that 'anticipation' is present in these pedigrees and that the recurrence of thyroid cancer in the family is not due to a screening bias.

Discussion

A minority of human cancers is recognized as inherited with an autosomal-dominant form of transmission, and the gene responsible for the disease has been characterized (Turnbull & Hodgson 2005). Nevertheless, clustering of a given cancer in the same family is also frequent in those cancers, the majority, that are

Table 3 Demographic and disease characteristics of FNMTC patients (both Italian and Greek cohorts) with parent–child relationship

Parameters	First generation ($n=22$)	Second generation ($n=25$)	*P*
Gender: *n* (%)			0.02[a]
Male	1 (4.8)	8 (32)	
Female	21 (95.2)	17 (68)	
Tumor diameter (mm)			0.7[b]
Mean ± S.D.	15.7 + 11.9	16.9 + 15.4	
Median	13	17	
Multicentricity: *n* (%)			0.003[a]
Yes	4 (18.1)	16 (64)	
No	18 (81.9)	9 (36)	
Bilaterality: *n* (%)			0.01[a]
Yes	2 (9)	11 (44)	
No	20 (91)	14 (56)	
Tumor extention: *n* (%)			0.5[c]
Intrathyroidal	17 (77.3.)	17 (68)	
Extrathyroidal	5 (22.7)	8 (32)	
Metastases: *n* (%)			0.02[a]
Yes	1 (4.5)	8 (32)	
No	21 (95.5)	17 (68)	
Outcome: *n* (%)			0.04[c]
Cured	18 (81.8)	15 (60)	
Not cured	2 (9.1)	10 (40)	
Tumor-related death	2 (9.1)	0	
Recurrences: *n* (%)			0.3[a]
Yes	1 (4.5)	4 (16)	
No	21 (95.5)	21(84)	
Follow-up (months)	63.7 + 77.7	48.6 + 35.7	0.3[b]

[a]Fisher's exact test.
[b]By Mann–Whitney *U* test.
[c]By χ^2 test.

usually considered sporadic and where a predisposing gene is not discovered. This is also the case of FNMTC, whose prevalence has been reported in up to 10% in different series (Stoffer *et al*. 1986, Loh 1997), and is one of the human cancers with higher risk in close relatives (Hemminki *et al*. 2005). In a large population-based analysis (Goldgar *et al*. 1994), among 399,786 first-degree relatives of index cancer patients, the authors found a ninefold increase in risk of non-medullary thyroid cancer, the highest among all cancer types. Similarly, Hemminki *et al*. (2005) in their population-based study of the Sweden cancer registry found that for an individual, the risk of PTC was 3.21 and 6.24 respectively, when his/her parent and his/her sibling were diagnosed with thyroid cancers.

Several studies (Alsanea *et al*. 2000, Uchino *et al*. 2002, Triponez *et al*. 2006) reported that compared with sporadic PTCs, FNMTCs are usually more aggressive. At variance with these studies, other authors (Loh 1997, Maxwell *et al*. 2004) have reported no differences in the clinical behavior of sporadic and familial PTCs. In our series, there was a marginal trend to higher aggressiveness of FNMTC which were more frequently multifocal at presentation and exhibited more frequent recurrences and worse outcome during follow-up.

The demonstration of the real existence of inherited FNMTC is particularly difficult when compared with other human cancers, due to some peculiar features of the thyroid gland. Firstly, thyroid cancer is frequently found within uni- or multinodular goiter that *per se* is recognized as a familial disease (Krohn *et al*. 2005). In this setting, thyroid cancer may arise from somatic mutations in the background of a long-standing familial goiter. Second, the diagnosis of thyroid cancer is particularly frequent after the introduction of neck ultrasound in clinical practice, as demonstrated by the finding that thyroid cancer is the human cancer at the largest increase in the last 10 years in USA, Australia, and Europe (Burgess 2002, Leenhardt *et al*. 2004, AIRT Working group 2006, Davies & Welch 2006, Capezzone *et al*. 2007). In some malignancies, as in medullary thyroid cancer without germline RET (rearranged during transfectron) proto-oncogene mutations, the definition of familial disease is based on the presence of four or more affected family members (Mulligan *et al*. 1995). At variance with this definition, several authors define FNMTC as the presence of two or more first-degree relatives affected by differentiated thyroid cancer. However, the presence of only two affected members in kindred may represent a fortuitous association of the disease, as suggested by Charkes (2006), who applied an exact probability measure to a series of first-degree family members with FNMTC. According to his mathematical simulation, 62–69% of 2-hit families are sporadic occurrences and thus, only families with more than three affected first-degree relatives should be considered for clinical and genetic investigations of FNMTC. Deliberately, we considered in this study all pedigrees of our center, including those with only two affected members (the large majority), just to ascertain whether, even in them it was possible to detect peculiar clinical features that might, at least indirectly, suggest a true familial background rather than a fortuitous association of sporadic cases. Indeed, compared with their parents, patients in the second generation were significantly younger at diagnosis and, after ruling out the bias of screening effect, had younger age at disease onset. In addition, tumors of the second generation were more advanced at presentation, including multicentricity, bilaterality, and lymph node metastases and had worst outcome at follow-up. Interestingly, the mean diameter of the primary tumors in family members diagnosed with thyroid cancer after the diagnosis in the proband was not different from the mean diameter of the proband tumors. If the tumors were discovered by screening, one would expect to find mainly microcarcinomas, as in case of autoptic studies or ultrasound series (Harach *et al*. 1985, Mazzaferri & Massoll 2002). The above features are consistent with the so-called phenomenon of 'genetic anticipation' (McInnis 1996). This concept was developed in the 19th century by Morel (1857) in his *Traitè des Degenèrescences* and indicates the occurrence of a disease at earlier age and increased aggressiveness in successive generations. The concept of genetic anticipation has gained new attention in the last decades and has been fully demonstrated for several inherited benign and malignant disorders (Ashizawa *et al*. 1992, Ranen *et al*. 1995, Horwitz *et al*. 1996, Polito *et al*. 1996, Golden *et al*. 1999, Dagan & Gershoni-Baruch 2002, Vulliamy *et al*. 2004, Westphalen *et al*. 2005, Yaturu *et al*. 2005, Auer *et al*. 2007). In some of them, such as Huntington disease (Ranen *et al*. 1995) or dyskeratosis congenita (Vulliamy *et al*. 2004), a molecular mechanism possibly underlying 'anticipation' has been recognized (unstable trinucleotide repeat expansion in Huntington's disease and TERC (telomerase RNA component) mutation in congenital dyscheratosis). As far as FNMTC is concerned, no candidate genetic alterations has been discovered, apart from susceptibility loci found in a few pedigrees with FNMTC: the locus TCO (thyroid tumors with cell oxyphilia) on 19p13.2, the locus PRN1 on 1q21, the locus NMTC1 on 2q21 (Canzian *et al*. 1998, Malchoff *et al*. 2000, McKay *et al*. 2001) and, although not confirmed, the locus MNG1 on 14q32

(Bignell *et al*. 1997). In addition, we have recently demonstrated in a series of patients with familial papillary thyroid cancer (including also some patients of the present study), an imbalance of the telomere–telomerase complex at the germline level, consisting of short telomeres, increased telomerase copy number, and expression when compared with sporadic papillary thyroid cancer (Capezzone *et al*. 2008). This alteration may contribute (among other as yet unknown abnormalities) to confer genetic predisposition to develop FNMTC and might be involved in the anticipation phenomenon.

In conclusion, this study provides clinical evidence of 'anticipation' in FNMTC, possibly suggesting the inheritance of this familial form of thyroid cancer even when only two members of a family are affected. In view of some features of aggressiveness (particularly in the second generation) at diagnosis and during follow-up, patients with FNMTC should probably be offered radical initial treatment, including total thyroidectomy with central neck dissection, and post-surgical radioiodine ablation as a routine procedure regardless of the primary tumor size.

Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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References

AIRT Working Group 2006 Italian cancer figures-report 2006:1. Incidence, mortality and estimates. *Epidemiologia e Prevenzione* **30** 8–10, 12–28, 30–101.

Alsanea O, Wada N, Ain K, Wong M, Taylor K, Ituarte PH, Treseler PA, Weier HU, Freimer N, Siperstein AE *et al.* 2000 Is familial non-medullary thyroid carcinoma more aggressive than sporadic thyroid cancer? A multicenter series. *Surgery* **128** 1043–1051.

Ashizawa T, Dunne CJ, Dubel JR, Perryman MB, Epstein HF, Boerwinkle E & Hejtmancik JF 1992 Anticipation in myotonic dystrophy: statical verification based in clinical and haplotype findings. *Neurology* **42** 1871–1877.

Auer RL, Dighiero G, Goldin LR, Syndercombe-Court D, Jones C, McElwaine S, Newland AC, Fegan CD, Caporaso N & Cotter FE 2007 Trinucleotide repeat dynamic mutation identifying susceptibility in familial and sporadic chronic lymphocytic leukaemia. *British Journal of Haematology* **136** 73–79.

Bignell GR, Canzian F, Shayeghi M, Stark M, Shugart YY, Biggs P, Mangion J, Hamoudi R, Rosenblatt J, Buu P *et al.* 1997 Familial non-toxic multinodular thyroid goiter locus maps to chromosome 14q but does not account for familial nonmedullary thyroid cancer. *American Journal of Human Genetics* **61** 1123–1130.

Burgess JR 2002 Temporal trends for thyroid carcinoma in Australia: an increasing incidence of papillary thyroid carcinoma (1982–1997). *Thyroid* **12** 141–149.

Canzian F, Amati P, Harach HR, Kraimps JL, Lesueur F, Barbier J, Levillain P, Romeo G & Bonneau D 1998 A gene predisposing to familial thyroid tumors with cell oxyphilia maps to chromosome 19p13.2. *American Journal of Human Genetics* **63** 1743–1748.

Capezzone M, Morabito E, Bellitti P, Giannasio P, De Sanctis D & Bruno R 2007 Increasing incidence of thyroid cancer in Basilicata: an italian study. *Journal of Endocrinological Investigation* **30** 507–512.

Capezzone M, Cantara S, Marchisotta S, Filetti S, De Santi MM, Rossi B, Ronga G, Durante C & Pacini F 2008 Short telomeres, hTERT gene amplification and increased telomerase activity in the blood of familial non-medullary thyroid cancer patients. *Journal of Clinical Endocrinology and Metabolism* **93** 3950–3957.

Charkes ND 2006 On the prevalence of familial nonmedullary thyroid cancer. *Thyroid* **8** 857–858.

Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Sherman SI & Tuttle RM 2006 The American Thyroid Association Guidelines Taskforce Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* **16** 109–142.

Dagan E & Gershoni-Baruch R 2002 Anticipation in hereditary breast cancer. *Clinical Genetics* **62** 147–150.

Davies L & Welch HG 2006 Increasing incidence of thyroid cancer in the United States, 1973–2002. *Journal of the American Medical Association* **295** 2164–2167.

Frich L, Glattre E & Akslen LA 2001 Familial occurrence of non-medullary thyroid cancer: a population-based study of 5673 first-degree relatives of thyroid cancer patients from Norway. *Cancer Epidemiology, Biomarkers and Prevention* **10** 113–117.

Golden LR, Sgambati M, Marti GE, Fontaine L, Ishibe N & Caporaso N 1999 Anticipation in familial chronic lymphocytic leukemia. *American Journal of Human Genetics* **65** 265–269.

Goldgar DE, Easton DF, Cannon-Albright LA & Skolnick MH 1994 Systemic population-based assessment of cancer risk in first-degree relatives of cancer probands. *Journal of the National Cancer Institute* **86** 1600–1608.

Grossman RF, Tu SH, Duh QY, Siperstein AE, Novosolov F & Clark OH 1995 Familial nonmedullary thyroid cancer. An emerging entity that warrants aggressive treatment. *Archives of Surgery* **130** 892–897.

Harach HR, Franssila KO & Wasenius VM 1985 Occult papillary carcinoma of the thyroid. A "normal" finding in Finland. A systematic autopsy study. *Cancer* **56** 531–538.

Hay ID, Thompson GB, Grant CS, Bergstralh EJ, Dvorak CE, Gorman CA, Maurer MS, McIver B, Mullan BP, Oberg AL *et al.* 2002 Papillary thyroid carcinoma managed at the Mayo Clinic during six decades 1940–1999): temporal trends in initial therapy and long-term outcome in 2444 consecutively treated patients. *World Journal of Surgery* **26** 879–885.

Hemminki K & Li X 2003 Familial risk of cancer by site and histopathology. *International Journal of Cancer* **103** 105–109.

Hemminki K, Eng C & Chen B 2005 Familial risks for nonmedullary thyroid cancer. *Journal of Clinical Endocrinology and Metabolism* **90** 5747–5753.

Horwitz M, Goode EL & Jarvik GP 1996 Anticipation in familial leukemia. *American Journal of Human Genetics* **59** 990–998.

Krohn K, Fuhrer D, Bayer Y, Eszlinger M, Brauer V, Neumann S & Paschke R 2005 Molecular pathogenesis of euthyroid and toxic multinodular goiter. *Endocrine Reviews* **26** 504–524.

Leenhardt L, Bernier MO, Boin-Pineau MH, Conte Devolx B, Maréchaud R, Niccoli-Sire P, Nocaudie M, Orgiazzi J, Schlumberger M, Wémeau JL *et al.* 2004 Advances in diagnostic practices affect thyroid cancer incidence in France. *European Journal of Endocrinology* **150** 133–139.

Loh KC 1997 Familial nonmedullary thyroid carcinoma: a meta-review of case series. *Thyroid* **7** 107–113.

Malchoff CD, Sarfarazi M, Tendler B, Forouhar F, Whalen G, Joshu V, Arnold A & Malchoff DM 2000 Papillary thyreoid carcinoma associated with papillary renal neoplasia: genetic linkage analysis of a distict heritable tumor sindrome. *Journal of Clinical Endocrinology and Metabolism* **85** 1758–1764.

Maxwell EL, Hall FT & Freeman JL 2004 Familial non-medullary thyroid cancer: a matched-case control study. *Laryngoscope* **114** 2182–2186.

Mazzaferri EL & Massoll N 2002 Management of papillary and follicular (differentiated) thyroid cancer: new paradigms using recombinant human thyrotropin. *Endocrine-Related Cancer* **9** 227–247.

McInnis MG 1996 Anticipation: an old idea in new genes. *American Journal of Human Genetics* **59** 973–979.

McKay JD, Lesueur F, Jonard L, Pastore A, Williamson J, Hoffman L, Burgess J, Duffield A, Papotti M, Stark M *et al.* 2001 Localization of a susceptibility gene for familial nonmedullary thyroid carcinoma to chromosome 2q21. *American Journal of Human Genetics* **69** 440–446.

Morel BA 1857 *Traitè des Dègènèrescences*. Paris: JB Bailliere.

Mulligan LM, Marsh DJ, Robinson BG, Schuffenecker I, Zedenius J, Lips CJ, Gagel RF, Takai SI, Noll WW, Fink M *et al.* 1995 Genotype–phenotype correlation in multiple endocrine neoplasia type 2: report of the international RET Mutation Consortium. *Journal of Internal Medicine* **238** 343–346.

Musholt TJ, Musholt PB, Petrich T, Oetting G, Knapp WH & Klempnauer J 2000 Familial papillary thyroid carcinoma: genetics, criteria for diagnosis, clinical features and surgical treatment. *World Journal of Surgery* **24** 1409–1417.

Pacini F, Schlumberger M, Dralle H, Elisei R, Smit JA, Wiersinga W & the European Thyroid Cancer Taskforce 2006 European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. *European Journal of Endocrinology* **154** 787–803.

Pal T, Vogl FD, Chappuis PO, Tsang R, Brierley J, Renard H, Sanders K, Kantemiroff T, Bagha S, Golgar DE *et al.* 2001 Increased risk for nonmedullary thyroid cancer in the first degree relatives of prevalent cases of nonmedullary thyroid cancer: a hospital-based study. *Journal of Clinical Endocrinology and Metabolism* **86** 5307–5312.

Polito JM, Rees RC, Childs B, Mendeloff AI, Harris ML & Bayless TM 1996 Preliminary evidence for genetic anticipation in Crohn's disease. *Lancet* **347** 798–800.

Ranen NG, Stine OC, Abbott MH, Sherr M, Codori AM, Franz ML, Chao NI, Chung AS, Pleasant N, Callahan C *et al.* 1995 Anticipation and instability of IT-15 (CAG)n repeats in parent–offspring pairs with Huntington disease. *American Journal of Human Genetics* **57** 593–602.

Stoffer SS, Van Dyke DL & Bach JV 1986 Familial papillary carcinoma of the thyroid. *American Journal of Medical Genetics* **25** 775–782.

Sturgeon C & Clark OH 2005 Familial nonmedullary thyroid cancer. *Thyroid* **15** 588–593.

Triponez F, Wong M, Sturgeon C, Caron N, Ginzinger DG, Segal MR, Kebebew E, Duh QY & Clark OH 2006 Does familial non-medullary thyroid cancer adversely affect survival? *World Journal of Surgery* **30** 787–793.

Turnbull C & Hodgson S 2005 Genetic predisposition to cancer. *Clinical Medicine* **5** 491–498.

Uchino S, Noguchi S, Kawamoto H, Yamashita H, Watanabe S, Yamashita H & Shuto S 2002 Familial non-medullary thyroid carcinoma characterized by multifocality and a high recurrence rate in a large study population. *World Journal of Surgery* **26** 897–902.

Vieland VJ & Huang J 1998 Statistical evaluation of age-at-onset anticipation: a new test and evaluation of its behavior in realistic applications. *American Journal of Human Genetics* **62** 1217–1227.

Vulliamy T, Marrone A, Szydlo R, Walne A, Mason PJ & Dokal I 2004 Disease anticipation is associated with progressive telomere shortening in families with dyskeratosis congenita due to mutations in TERC. *Nature Genetics* **36** 447–449.

Westphalen AA, Russell AM, Buser M, Berthod CR, Hutter P, Plasilova M, Mueller H & Heinimann K 2005 Evidence for genetic anticipation in hereditary non-polyposis colorectal cancer. *Human Genetics* **116** 461–465.

Yaturu S, Bridges JF & Dhanireddy RR 2005 Preliminary evidence of genetic anticipation in type 2 diabetes mellitus. *Medical Science Monitor* **11** 262–265.